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Dkt. 57477-A-PCT-US/JPW/MVM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Thomas M. Jessell et al.

Serial No.: 09/820,598 Group Art Unit: 1653

Filed: March 29, 2001 Examiner: K. Carlson, Ph.D.

For: GENE ENCODING MNR2 AND USES THEREOF

1185 Avenue of the Americas
New York, New York 10036
March 31, 2005

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION UNDER 37 C.F.R. §1.181(a)
TO WITHDRAW HOLDING OF ABANDONMENT

This is a Petition under 37 C.F.R. §1.181(a) to withdraw the holding of abandonment as set forth in a Notice of Abandonment issued January 31, 2005 by the United States Patent and Trademark Office ("PTO") in connection with the above-identified application. The January 31, 2005 Notice indicates that the subject application was abandoned for applicants' alleged failure to timely file a proper reply to the Office Action mailed on July 14, 2004. A copy of the January 31, 2005 Notice is attached as **Exhibit I**. 37 C.F.R. §1.181(f) provides a period of two months from the mailing date of the Notice to file a petition. Therefore, a response to the January 31, 2005 Notice is due March 31, 2005. Accordingly, this Petition is being timely filed.

A petition under 37 C.F.R. §1.181(a) requires that applicants submit: (1) a statement of the facts involved; (2) the point(s) to be reviewed; and (3) the action requested.

Statement of the Facts

An Office Action was issued in connection with the subject application on February 11, 2004, a copy of which is attached hereto as **Exhibit II**.

In response to the February 11, 2004 Office Action, applicants timely submitted a single piece of correspondence entitled "Amendment In Response To February 11, 2004 And Information Disclosure Statement" (hereinafter "Amendment and IDS") on May 11, 2004. Applicants attach as **Exhibit III** a copy of this document, including Exhibits A-F. The Amendment is signed at page 39 and, also on that page, includes a signed certificate of mailing dated May 11, 2004. Applicants note that Exhibits 1-58 submitted to the PTO with the Amendment and IDS are references to have been made of record and have not been included herewith. The Amendment and IDS was received by the PTO on May 13, 2004 as evidenced by the copy of the return postcard date-stamped received on May 13, 2004 by the Office of Initial Patent Examination ("OIPE"), a copy of which is attached hereto as **Exhibit IV**.

On May 25, 2004, a Notice of Non-Compliant Amendment (37 C.F.R. §1.121) was issued by the PTO in connection with the subject application, a copy of which is attached hereto as **Exhibit V**.

In response to the May 25, 2004 Notice, applicants timely submitted a Communication In Response To May 25, 2004 Notice of Non-Compliant Amendment (37 CFR 1.121) on June 25, 2004.

Applicants attach as **Exhibit VI** a copy of the Communication, including a copy of the Notice as Exhibit A to the Communication. The Communication is signed and includes a signed certificate of mailing dated June 25, 2004. The Communication was received by the PTO on June 29, 2004 as evidenced by the copy of the return postcard date-stamped received on June 29, 2004 by OIPE, a copy of which is attached hereto as **Exhibit VII**. In the June 25, 2004 Communication, applicants made of record a June 16, 2004 telephone conference between Maria V. Marucci, Esq. of the undersigned's firm and Legal Instruments Examiner Marissa Blyther, wherein Examiner Blyther stated that (i) the May 25, 2004 Notice was sent in error and (ii) no response thereto was required.

On July 14, 2004, a Notice was issued by the Examiner in connection with the subject application. A copy of the July 14, 2004 Notice is attached as **Exhibit VIII**. The July 14, 2004 Notice required applicants to submit a "corrected" version of the Amendment and IDS. A reply to the July 14, 2004 Notice was due August 14, 2004, which deadline was extendible until January 14, 2005.

In an August 13, 2004 telephone conference between John P. White, Esq., an attorney of record, and Mark Polutta, Esq. of the PTO's Office of Patent Legal Administration, Mr. Polutta stated that (i) some of the claim status identifiers used by applicants in the Amendment and IDS were not those set forth under the revised amendment practice rules, i.e. 37 C.F.R. §1.121, (ii) the July 14, 2004 Notice would be withdrawn, and (iii) a response to the Notice was <u>not</u> required. Mr. Polutta

further stated that a new communication would be sent by the PTO regarding noncompliance of the May 11, 2004 Amendment with revised Rule 121.

On August 16, 2004, applicants timely submitted a signed Communication In Response To July 14, 2004 Notice to make of record the contents of the August 13, 2004 telephone conference between Mr. White and Mr. Polutta, wherein Mr. Polutta stated, in relevant part, that a response to the July 14, 2004 Notice was not required. Applicants attach as **Exhibit IX** a copy of the August 16, 2004 Communication, including a copy of the Notice as Exhibit A thereof. The Communication was received by the PTO on August 19, 2004 as evidenced by the copy of the return postcard date-stamped received on August 19, 2004 by OIPE, a copy of which is attached hereto as **Exhibit X**.

A Notice of Abandonment was issued by the PTO on January 31, 2005 in connection with the subject application. The Notice of Abandonment cites applicants' alleged failure to respond to the July 14, 2004 Notice as the reason for abandonment.

Points to be Reviewed

Again, in the January 31, 2005 Notice of Abandonment, the Examiner stated that this application is abandoned in view of applicants' alleged failure to timely file a proper reply to the Office letter mailed on July 14, 2004. The Examiner stated that a reply was received on August 18, 2004 but it does not constitute a proper reply, or a bona fide attempt at a proper

reply, to the non-final rejection. The Examiner stated that applicants' representative John P. White signed the transmittal authorizing fees filed May 13, 2004 (understood to mean May 11, 2004) and the Information Disclosure Statement filed May 13, 2004 (understood to mean May 11, 2004), but did not sign the Amendment filed May 13, 2004 (understood to mean May 11, 2004). The Examiner stated that it is not clear which if any of applicants' representatives made the amendments, or who takes responsibility for the amendments. The Examiner stated that therefore, the Notice mailed July 14, 2004 stands.

The Examiner also stated that each piece of correspondence must be signed in accordance with Rule 1.4(d)(1).

In response, applicants respectfully note that the May 11, 2004 Amendment and IDS fully complies with 37 C.F.R. §1.4(d)(1) and that the July 14, 2004 Notice was issued in error.

37 C.F.R. §1.4(d)(1) provides that:

> "Each *piece of correspondence*, except as provided in paragraphs (e) and (f) of this section, filed in an application, patent file, or other proceeding in the Office which requires a person's signature, must be an original, that is, have an original signature personally signed in permanent ink by that person." [emphasis added].

Applicants note the following facts regarding the Amendment and IDS: (i) the title of that document is "Amendment In Response to February 11, 2004 Office Action And Information Disclosure Statement"; (ii) the document includes two portions, one directed to amending the application and the other to making references of record; (iii) the document has one header and continuous page numbers; and (iv) the signature of John P. White and the signed certificate of mailing follow a section of the document entitled "Summary" which refers to both the amendment and the information disclosure statement portions of the document. Applicants direct the Examiner to the first sentence of the last paragraph on page 39 of the Amendment and IDS which recites: "No fee, other than the $180.00 fee for submitting an Information Disclosure Statement under 37 C.F.R. §1.97(c)(2), is deemed necessary in connection with the filing of this Amendment" [emphasis added]. Therefore, applicants maintain that the signature and certificate of mailing at the end of the Amendment and IDS are directed to all portions of the document, including both the amendment and information disclosure statement portions (and not merely the information disclosure statement portion alone as the Examiner asserts).

Applicants maintain that in issuing the July 14, 2004 Notice, the Examiner construed 37 C.F.R. §1.4(d)(1) in a manner devoid of any support in the law or regulations as embodied in the M.P.E.P. That is, rule 1.4 requires a single signature for "each piece of correspondence" submitted to the PTO. The Examiner has failed to cite, and applicants are unaware of, any rule or guideline precluding a piece of correspondence

from having more than a single portion such as an information disclosure statement or an amendment.

Therefore, applicants maintain that the May 11, 2004 Amendment and IDS constitutes one piece of correspondence requiring one signature under 37 C.F.R. §1.4. Accordingly, applicants maintain that the requirements of 37 C.F.R. §1.4 have been met, and the July 14, 2004 Notice was issued in error.

Finally, pursuant to 35 U.S.C. §154(b) and 37 C.F.R. §1.701 et seq., applicants maintain that they are entitled to an extension of the term of any patent which issues from the above-identified application, based, at least in part, on the PTO's failure, as set forth above, to respond to a reply under section 35 U.S.C. §132, i.e. the May 11, 2004 Amendment and IDS, within four (4) months after the date on which the reply was filed.

Actions Requested

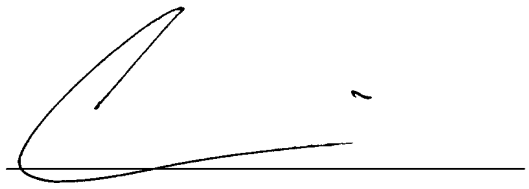
Applicants respectfully request that the PTO (i) withdraw the January 31, 2005 Notice of Abandonment, (ii) issue any communication which may be deemed necessary regarding the compliance of the claim listing portion of the May 11, 2004 Amendment and IDS with 37 C.F.R. §1.121; and (iii) adjust the patent term of any patent which issues from the subject application due to PTO delay.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants'

undersigned attorneys invite the Examiner to telephone either of them at the number provided below.

No fee is deemed necessary in connection with the filing of this Petition. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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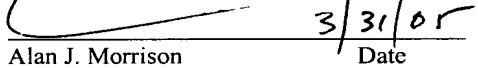
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Petitions, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



3/31/05

Alan J. Morrison
Reg. No. 37,399

Date

0575/57477-A-PCT-US JPW

Notice of Abandonment	Application No. 09/820,598	Applicant(s) JESSELL ET AL.	
	Examiner Karen Cochrane Carlson, Ph.D.	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of: Petition to Revive: 3/31/05 on

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *14 July 2004*.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 (a) to the final rejection.
   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).
   (c) ☒ A reply was received on *18 August 2004* but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below). FEB 8 2005
   (d) ☐ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $_____ is insufficient. A balance of $_____ is due.
   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d), is $_____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☒ The reason(s) below:

See Continuation Sheet

Petitions to revive under 37 CFR 1.137(a) or (b), or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

Applicants: Thomas Jessell et al.
U.S. Serial No.: 109/820,598
Filed: March 29, 2001
Exhibit I

Item 7 - Other reasons for holding abandonment: Applicants have filed a Miscellaneous Incoming Letter on Aug 19, 2004 setting forth an alleged discussion Applicants had with Mark Polutta of PTO's OPLA on August 13, 2004. Because the response was not a response to the Notice, this MIL did not come to the Examiner's attention until she was ready to abandon the case on Jan. 24, 2005. Mr. Polutta may advise Applicants on procedure, but he has no authority to remove an Office action with a shortened statutory period for response. Further the Examiner has discussed (in August, 2004 and again Jan. 24, 2005) the issue of unsigned documents with Mr. Polutta and we are in agreement that each piece of correspondence must be signed in accordance with Rule 1.4(d)(1): "Each piece of correspondence, except a provided in paragraphs (e) and (f) of this section, filed in an application, patent file, or other proceeding in theOffice which requires a person's signature, must: (i) Be an original, that is, have an original signature personally signed in permanent ink by that person."

Applicants representative John P. White signed the transmittal authorizing fees filed May 13, 2004, signed the Information Disclosure Statement filed May 13, 2004, but did not sign the amendment filed May 13, 2004. Thus, it is not clear which if any of of Applicants representatives made the amendments, or who takes responsibility for the amendments. Therefore, the Notice mailed July 14, 2004 stand

It is not understood why Applicants have allowed this application for patent go abandoned over an unexecuted amendment. The Examiner gave a courtesy call to John P. White on June 29, 2004 to provide a signed copy of the amendment. A woman named Maria Marucci returned the phone call and presented herself as an attorney having authority in the file. In fact, she is not recognized by the PTO as havin authority to practice before the office. Ms. Marucci argued with me (the Examiner) that their office does this all of the time and that I was wrong to insist that the amendment be signed. I begged to differ, because the reason for the courtesy call was because omission of a signature on a document was unusual and had not been an issue that I have had with John P. White in the 13 yrs that I have been prosecuting applications with him. Ms. Marucci asked where I got the authority to insist that the amendment be signed. I told her that this was standard operating procedure and cited her Rule 1.4.

Ms.Marucci then called SPE Jon Weber regarding this situation. Dr. Weber also told Ms. Marucci that the amendment had to be signed and cited Rule 1.4. The Notice was sent to Applicants July 14, 2004.

On August 12, 2004, Mark Polutta from the PTO's OPLA provided a courtesy call to the Examiner regarding a conversation he had with Ms Marucci. Ms. Marucci had telephoned him and argued with him that no signature is necessary on the amendment. Mr. Polutta informed m that I was correct to insist that the amendment had to be signed and that sending the Notice was appropriate.

On January 25, 2005, an e-mail exchange with Magdalene Greenleif, editor of the MPEP, confirmed that each piece of correspondence must be signed, in accordance to Rule 1.4.

No interview summaries of these conversations have been provided to make of record these conversation because Ms Marucci is not authorized to practice before the PTO and because the merits of the case were not discussed. The conversation dates are derived from th Examiner's phone logs.

It is also noted that Applicants have missed the deadline for response for the Notice of Non-compliant Amendment mailed May 25, 2004.

Karen Cochrane Carlson, PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/820,598	03/29/2001	Thomas M. Jessell	57477-A-PCT-US/JPW/MVM	5690

7590 01/31/2005

Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
CARLSON, KAREN C	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 01/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

5747-A-PCT-US JPW

Application No.	Applicant(s)	
09/820,598	JESSELL ET AL.	
Examiner	**Art Unit**	
Karen Cochrane Carlson, Ph.D.	1653	

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 ~~U.S.C. § 133~~).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

FEB 17 2004

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. ~~11, 453 O.G.~~ 213.

3 mo: 5-11-2004
4 mo: 6-11-2004
5 mo: 7-11-2004
6 mo: 8-11-2004

Disposition of Claims

4)☒ Claim(s) *27,38,45,48-50,52,60 and 125-130* is/are pending in the application.

4a) Of the above claim(s) *38,129 and 130* is/are withdrawn from consideration.

5)☒ Claim(s) *126* is/are allowed.

6)☒ Claim(s) *27,45,48-50,52,60,127 and 128* is/are rejected.

7)☒ Claim(s) *125* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicants: Thomas Jessell et al.
U.S. Serial No.: 109/820,598
Filed: March 29, 2001
Exhibit II

Applicant's election with traverse of Invention II, Claims 27, 48, and 125-128, in the paper filed November 17, 2003 is acknowledged. The traversal is on the ground(s) that it would not be an undue burden to search methods of treatment using the nucleic acid encoding MNR2 and antibodies against MNR2. This is not found persuasive because the method of Claim 38 utilizes a different product, that is the nucleic acid encoding MNR2, and is therefore patentably distinct. The antibodies of Claims 129 and 130 are different products.

Upon examination of the MNR2 protein, the full-length MNR2 protein is allowable. Therefore, the Examiner has examined the methods of treatment utilizing the MNR2 protein, Claims 45, 49, 50, 52, and 60, in accordance with In re Ochiae.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-26, 28-37, 39-44, 46, 47, 51, 53-59, and 61-124 have been canceled. Claims 38, 129, and 130 has been withdrawn from further consideration by the Examiner because these claims are drawn to non-elected inventions. Claims 27, 45, 48, 49, 50, 52, 60, and 125-128 are under examination.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27, 45, 48, 49, 50, 52, 60, 127, and 128 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 is not comprehensible. It is not clear what a homeobox motor neuron restricted pattern protein is. The acronym MNR2 is used, making this name unclear. MNR2 is not defined by structure or by function. Thus, the protein is not defined such that one skilled in the art could recognize the limitations of the claim. See also the dependent claims.

In Claim 45, it is not clear how only a single somatic motor neuron will be affected by the systemic administration of MNR2. Also, what is the somatic motor neuron being differentiated into?

In Claim 49, it is not clear what abnormality is associated with a lack of one or more normally functioning motor neurons. Also, the phrase "effective to a generate" is awkward. See also Claim 50, 52.

Claim 50 is indefinite because the neurodegenerative disease is not stated. Claims 52 and 60 also lack specific diseases to be treated.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 127, and 128 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not provide written description of mouse, rat, or human MNR2 protein.

Claim 27, 45, 48, 49, 50, 52, 60, 127, and 128 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for MNR2 comprising SEQ ID NO: 1, does not reasonably provide enablement for all MNR2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In *Ex parte Forman* (230 USPQ 546) the Board considered the issue of enablement in molecular biology. The Board held that the following factors should be considered to determine whether the claimed invention would require of the skilled artisan undue experimentation:

1) Quantity of experimentation necessary: It would require undue experimentation to acquire all MNR2 across all species, to the scope of the claims.

2) Amount of direction or guidance presented: At page 45 and 47+ of the specification, routineers in the field are invited to find for themselves, the scope of the MNR2 proteins as claimed, via nucleic acid probes, or antibody assays.

3) Presence or absence of working examples: None.

4) Nature of the invention; 5) State of the prior art; 6) Relative skill of those in the art: The invention is highly technical and the MNR2 protein is not recognized in the prior art. Those working in the art are highly skilled.

7) Predictability or unpredictability of the art: Finding a protein that is involved in the differentiation of neurons is highly unpredictable.

8) Breadth of the claims: The claims are very broad.

For all of these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention.

Claims 45, 49, 50, 52, and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These Claims are drawn to methods of treating neurological diseases/injuries by administering the MNR2 protein systemically to a subject, thus causing differentiation of neuronal precursor cells.

Simply, these methods are not art-recognized such that there could be a nexus between other prior art proteins and the treatment of neurological diseases/injury and MNR2.

In *Ex parte Forman* (230 USPQ 546) the Board considered the issue of enablement in molecular biology. The Board held that the following factors should be considered to determine whether the claimed invention would require of the skilled artisan undue experimentation:

1) Quantity of experimentation necessary: It would require undue experimentation to determine how one would treat diseases/injuries that are not known to be routinely treatable with a new protein that is involved with neuronal cell differentiation.

2) Amount of direction or guidance presented: Page 50+ provides a generic discussion of methods of treatment using protein, and these methods are not specific to neural abnormalities.

3) Presence or absence of working examples: None.

4) Nature of the invention; 5) State of the prior art; 6) Relative skill of those in the art: The invention is highly technical and the MNR2 protein is not recognized in the prior art. Those working in the art are highly skilled.

7) Predictability or unpredictability of the art: Finding a protein that is involved in the differentiation of neurons is highly unpredictable; using the protein to differentiate neuronal cells in vivo is highly unpredictable.

8) Breadth of the claims: The claims are very broad.

For all of these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention.

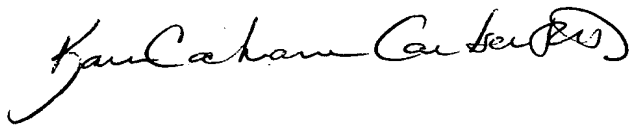
Claim 125 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 126 is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cochrane Carlson, Ph.D. whose telephone number is 571-272-0946. The examiner can normally be reached on 7:00 AM - 4:00 PM, off alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.



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KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

Notice of References Cited

Application/Control No.	Applicant(s)/Patent Under Reexamination	
09/820,598	JESSELL ET AL.	
Examiner	Art Unit	Page 1 of 1
Karen Cochrane Carlson, Ph.D.	1653	

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
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FOREIGN PATENT DOCUMENTS

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NON-PATENT DOCUMENTS

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	X	

\ copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
ates in MM-YYYY format are publication dates. Classifications may be US or foreign.

NOTICE OF OFFICE PLAN TO CEASE SUPPLYING COPIES OF CITED U.S. PATENT REFERENCES WITH OFFICE ACTIONS, AND PILOT TO EVALUATE THE ALTERNATIVE OF PROVIDING ELECTRONIC ACCESS TO SUCH U.S. PATENT REFERENCES

Summary

The United States Patent and Trademark Office (Office or USPTO) plans in the near future to: (1) cease mailing copies of U.S. patents and U.S. patent application publications (US patent references) with Office actions except for citations made during the international stage of an international application under the Patent Cooperation Treaty and those made during reexamination proceedings; and (2) provide electronic access to, with convenient downloading capability of, the US patent references cited in an Office action via the Office's private Patent Application Information Retrieval (PAIR) system which has a new feature called "E-Patent Reference." Before ceasing to provide copies of U.S. patent references with Office actions, the Office shall test the feasibility of the E-Patent Reference feature by conducting a two-month pilot project starting with Office actions mailed after December 1, 2003. The Office shall evaluate the pilot project and publish the results in a notice which will be posted on the Office's web site (www.USPTO.gov) and in the Patent Official Gazette (O.G.). In order to use the new E-Patent Reference feature during the pilot period, or when the Office ceases to send copies of U.S. patent references with Office actions, the applicant must: (1) obtain a digital certificate from the Office; (2) obtain a customer number from the Office, and (3) properly associate applications with the customer number. The pilot project does not involve or affect the current Office practice of supplying paper copies of foreign patent documents and non-patent literature with Office actions. Paper copies of references will continue to be provided by the USPTO for searches and written opinions prepared by the USPTO for international applications during the international stage and for reexamination proceedings.

Description of Pilot Project to Provide Electronic Access to Cited U.S. Patent References

On December 1, 2003, the Office will make available a new feature, E-Patent Reference, in the Office's private PAIR system, to allow more convenient downloading of U.S. patents and U.S. patent application publications. The new feature will allow an authorized user of private PAIR to download some or all of the U.S. patents and U.S. patent application publications cited by an examiner on form PTO-892 in Office actions, as well as U.S. patents and U.S. patent application publications submitted by applicants on form PTO/SB08 (1449) as part of an IDS. The retrieval of some or all of the documents may be performed in one downloading step with the documents encoded as Adobe Portable Document format (.pdf) files, which is an improvement over the current page-by-page retrieval capability from other USPTO systems.

Steps to Use the New E-Patent Reference Feature During the Pilot Project and Thereafter

Access to private PAIR is required to utilize E-Patent Reference. If you don't already have access to private PAIR, the Office urges practitioners, and applicants not represented by a practitioner, to take advantage of the transition period to obtain a no-cost USPTO Public Key Infrastructure (PKI) digital certificate, obtain a USPTO customer number, associate all of their pending and new application filings with their customer number, install no-cost software (supplied by the Office) required to access private PAIR and E-Patent Reference feature, and make appropriate arrangements for Internet access. The full instructions for obtaining a PKI digital certificate are available at the Office's Electronic Business Center (EBC) web page at: <http://www.uspto.gov/ebc/downloads.html>. Note that a notarized signature will be required to obtain a digital certificate.

To get a Customer Number, download and complete the Customer Number Request form, PTO-SB125, at: http://www.uspto.gov/web/forms/sb0125.pdf. The completed form can then be transmitted by facsimile to the Electronic Business Center at (703) 308-2840, or mailed to the address on the form. If you are a registered attorney or patent agent, then your registration number must be associated with your customer number. This is accomplished by adding your registration number to the Customer Number Request form. A description of associating a customer number with an application is described at the EBC web page at: http://www.uspto.gov/ebc/registration_pair.html.

The E-Patent Reference feature will be accessed using a new button on the private PAIR screen. Ordinarily all of the cited U.S. patent and U.S. patent application publication references will be available over the Internet using the Office's new E-Patent Reference feature. The size of the references to be downloaded will be displayed by E-Patent Reference so the download time can be estimated. Applicants and registered practitioners can select to download all of the references or any combination of cited references. Selected references will be downloaded as complete documents as Adobe Portable Document Format (.pdf) files. For a limited period of time, the USPTO will include a copy of this notice with Office actions to encourage applicants to use this new feature and, if needed, to take the steps outlined above in order to be able to utilize this new feature during the pilot and thereafter.

During the two-month pilot, the Office will evaluate the stability and capacity of the E-Patent Reference feature to reliably provide electronic access to cited U.S. patent and U.S. patent application publication references. While copies of U.S. patent and U.S. patent application publication references cited by examiners will continue to be mailed with Office actions during the pilot project, applicants are encouraged to use the private PAIR and the E-Patent Reference feature to electronically access and download cited U.S. patent and U.S. patent application publication references so the Office will be able to objectively evaluate its performance. The public is encouraged to submit comments to the Office on the usability and performance of the E-Patent Reference feature during the pilot. Further, during the pilot period registered practitioners, and applicants not represented by a practitioner, are encouraged to experiment with the feature, develop a proficiency in using the feature, and establish new internal processes for using the new access to the cited U.S. patents and U.S. patent application publications to prepare for the anticipated cessation of the current Office practice of supplying copies of such cited

references. The Office plans to continue to provide access to the E-Patent Reference feature during its evaluation of the pilot.

Comments

Comments concerning the E-Patent Reference feature should be in writing and directed to the Electronic Business Center (EBC) at the USPTO by electronic mail at eReference@uspto.gov or by facsimile to (703) 308-2840. Comments will be posted and made available for public inspection. To ensure that comments are considered in the evaluation of the pilot project, comments should be submitted in writing by January 15, 2004.

Comments with respect to specific applications should be sent to the Technology Centers' customer service centers. Comments concerning digital certificates, customer numbers, and associating customer numbers with applications should be sent to the Electronic Business Center (EBC) at the USPTO by facsimile at (703) 308-2840 or by e-mail at EBC@uspto.gov.

Implementation after Pilot

After the pilot, its evaluation, and publication of a subsequent notice as indicated above, the Office expects to implement its plan to cease mailing paper copies of U.S. patent references cited during examination of non provisional applications on or after February 2, 2004; although copies of cited foreign patent documents, as well as non-patent literature, will still be mailed to the applicant until such time as substantially all applications have been scanned into IFW.

For Further Information Contact

Technical information on the operation of the IFW system can be found on the USPTO website at http://www.uspto.gov/web/patents/ifw/index.html. Comments concerning the E-Patent Reference feature and questions concerning the operation of the PAIR system should be directed to the EBC at the USPTO at (866) 217-9197. The EBC may also be contacted by facsimile at (703) 308-2840 or by e-mail at EBC@uspto.gov.

Date: 12/1/03

Nicholas P. Godici

Nicholas P. Godici
Commissioner for Patents

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/820,598	03/29/2001	Thomas M. Jessell	57477-A-PCT-US/JPW/MVM	5690

7590 02/11/2004

Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
CARLSON, KAREN C	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Docket No. 0575/57477-A-PCT-US/JPW/MVM

In re application of: Thomas M. Jessell, et al.

Serial No.: 09/820,598 Examiner: K. Carlson, Ph.D.

Filed: March 29, 2001 Art Unit: 1653

For: GENE ENCODING MNR2 AND USES THEREOF

May 11, 2004

Commisioner for Patents
P.O. Box: 1450
Alexandria, VA 22313-1450
S I R:

Transmitted herewith is an amendment to the above-identified application.

__X__ Small entity status of this application under 37 C.F.R. § 1.9 and § 1.27 has been established by a verified statement previously submitted.

_____ a verified statement to establish small entity status under 37 C.F.R. § 1.9 and § 1.27 is enclosed.

_____ No additional fee is required.

The filing fee is calculated as follows:

	NUMBER AFTER AMEND-MENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		NUMBER OF EXTRA CLAIMS PRESENTED		RATE SMALL ENTITY	RATE OTHER ENTITY		FEE SMALL ENTITY	FEE OTHER ENTITY
Total Claims	14	-	* 42	=	*** 0	x	9	18	=	0	
Independent Claims	2	-	** 12	=	*** 0	x	43	86	=	0	
Multiple Dependent Claims(s) Presented For First Time:	____ Yes		__X__ No				145	290		0	
							TOTAL ADDITIONAL FEE			$ 0	

*If the "HIGHEST NUMBER PREVIOUSLY PAID FOR" is less than 20, write "20" in this space.

**If the "HIGHEST NUMBER PREVIOUSLY PAID FOR" is less than 3, write "3" in this space.

***If the difference between the "NUMBER AFTER AMENDMENT" and the "HIGHEST NUMBER PREVIOUSLY PAID FOR" is less than "0", write "0" in the space.

The "HIGHEST NUMBER PREVIOUSLY PAID FOR" (Total or Independent) is the highest of the "NUMBER AFTER AMENDMENT" in any prior amendment or the number of claims as originally filed.

____ Please charge Deposit Account No. _____ in the amount of $_____.

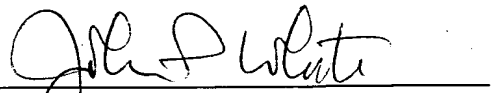
____ A check in the amount of $_____ is enclosed.
For a One-Month Extension of Time fee.

__X__ The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 03-3125 . Three copies of this sheet are enclosed.

__X__ Any filing fees under 37 C.F.R. §1.16 for the presentation of extra claims.

__X__ Any patent application processing fees under 37 C.F.R. §1.17.

Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicant
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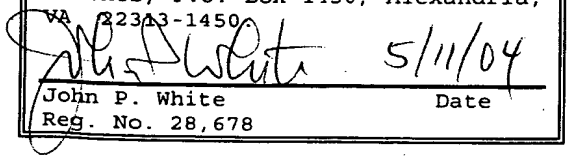
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



5/11/04

John P. White
Reg. No. 28,678

Date

Dkt. 57477-A-PCT-US/JPW/MVM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Thomas M. Jessell et al.

Serial No.: 09/820,598 Group Art Unit: 1653

Filed: March 29, 2001 Examiner: K. Carlson, Ph.D.

For: GENE ENCODING MNR2 AND USES THEREOF

1185 Avenue of the Americas
New York, New York 10036
May 11, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT IN RESPONSE TO FEBRUARY 11, 2004 OFFICE ACTION AND INFORMATION DISCLOSURE STATEMENT

This Amendment is submitted in response to a February 11, 2004 Office Action issued by the United States Patent and Trademark Office in connection with the above-identified application. A response to the February 11, 2004 Office Action is due May 11, 2004. Accordingly, this Amendment is being timely filed.

Please amend the subject application as follows:

In the specification:

On page 1, following the title, please amend the paragraph beginning at line 5 as follows:

-- This application is a continuation of PCT International Application No. PCT/US99/22517, filed 29 September 1999, designating the United States of America, which is a continuation-in-part and claims priority of U.S. Serial No. 09/162,524, filed September 29, 1998, now U.S. Patent No. 6,387,656 B1, issued May 14, 2002, the contents of which are hereby incorporated by reference into the present application.--

In the claims:

Please replace the claims with the listing of claims below.

--1. - 26. (previously cancelled) --

--27. (currently amended) An isolated protein ~~or fragment thereof encoded by an isolated nucleic acid or fragment thereof~~ comprising consecutive amino acids having the amino acid sequence set forth in SEQ ID NO:1 which encodes a homeobox motor neuron restricted pattern protein designated MNR2 or a fragment having the biological activity thereof.--

--28. - 37. (previously cancelled) --

--38. (withdrawn) A method of inducing differentiation of a somatic motor neuron which comprises expressing the protein of claim 27 in a neural progenitor cell, so as to thereby induce differentiation of the somatic motor neuron.--

--39. - 44. (previously cancelled) --

--45. (currently amended) A method of inducing differentiation of a neural progenitor cell into a somatic motor neuron in a subject comprising administering to the subject the protein of claim 27 in an amount effective to induce differentiation of the neural progenitor cell into a somatic motor neuron, so as to thereby induce differentiation of the neural

progenitor cell into a somatic motor neuron in the subject.--

--46. - 47. (previously cancelled) --

--48. (previously presented) A pharmaceutical composition comprising the protein of claim 27 and a pharmaceutically acceptable carrier.--

--49. (currently amended) A method for treating a subject afflicted with an abnormality associated with a lack of one or more normally functioning motor neurons which comprises introducing an amount of the pharmaceutical composition of claim 48 effective to [[a]] generate a somatic motor neuron from an undifferentiated motor neuron precursor cell in the subject, thereby treating the subject afflicted with the abnormality associated with the lack of one or more normally functioning motor neurons.--

--50. (previously presented) A method of treating a subject afflicted with a neurodegenerative disease which comprises introducing an amount of the pharmaceutical composition of claim 48 effective to generate a somatic motor neuron from an undifferentiated precursor motor neuron cell in the subject, thereby treating the subject afflicted with the neurodegenerative disease.--

--51. (previously cancelled) --

--52. (currently amended) A method of treating a subject afflicted with an acute nervous system injury which comprises introducing an amount of the pharmaceutical composition of claim 48 effective to [[a]] generate a motor neuron from an undifferentiated precursor motor neuron cell in the subject, thereby treating the subject afflicted with the acute nervous system injury.--

--53. - 59. (previously cancelled) --

--60. (previously presented) A method of treating a subject afflicted with a neuromuscular disease which comprises introducing an amount of the pharmaceutical composition of claim 48 effective to activate acetylcholine to activate muscle cells, so as to thereby treat the subject afflicted with the neuromuscular disease.--

--61. - 124. (previously cancelled) --

--125. (currently cancelled) --

--126. (allowed) An isolated protein comprising consecutive amino acids having the amino acid sequence set forth in SEQ ID NO: 1.--

--127. (previously presented) The protein of claim 27, wherein the protein is a vertebrate protein.--

--128. (currently amended) The protein of claim 127, wherein the protein is a chick~~, mouse, rat, or human~~ protein.--

--129. (withdrawn) A monoclonal antibody directed to an epitope of the protein of claim 128.--

--130. (withdrawn) A polyclonal antibody directed to an epitope of the protein of claim 128.--

REMARKS

Claims 27, 38, 45, 48, 49, 50, 52, 60 and 125-130 are pending in the subject application. The Examiner has indicated that claim 126 is allowed and withdrawn claims 38, 129 and 130 from further consideration in the subject application. Applicants have hereinabove cancelled claim 125 without prejudice or disclaimer. In addition, applicants have hereinabove amended claims 27, 45, 49, 52 and 128. Support for these amendments may be found inter alia in the specification as follows: claim 27: page 41, lines 17-23; Figure 10; claim 45: page 49, lines 36-37; and page 81, lines 4-5. The remaining changes to the claims merely introduce minor grammatical and format changes. These amendments do not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that claims 27, 45, 48, 49, 50, 52, 60 and 126-128 will be pending and under examination.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections have been overcome and respectfully request that the Examiner reconsider and withdraw the various grounds of rejection.

Restriction Requirement

The Examiner stated that applicants' election with traverse of Invention II, claims 27, 48 and 125-128, in the paper filed November 17, 2003 is acknowledged. The Examiner stated that applicants' traversal is not found persuasive.

The Examiner stated that upon examination of the MNR2 protein, the full-length MNR2 protein is allowable. Therefore, the Examiner stated that the Examiner has examined the methods of treatment utilizing the MNR2 protein, claims 45, 49, 50, 52, and 60, in accordance with *In re Ochiae*.

The Examiner stated that the requirement is still deemed proper and is therefore made final. The Examiner stated that claims 38, 129, and 130 has been withdrawn from further consideration because these claims are drawn to non-elected inventions. The Examiner stated that claims 27, 45, 48, 49, 50, 52, 60, and 125-128 are under examination.

In response, applicants respectfully traverse. Applicants respectfully request that the Examiner reconsider and withdraw the restriction requirement such that claims 38, 129 and 130 will be examined in connection with the subject application.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 27, 45, 48, 49, 50, 52, 60, 127, and 128 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention.

Claim 27

The Examiner stated that claim 27 is not comprehensible. The Examiner stated that it is not clear what a homeobox motor neuron restricted pattern is. The Examiner stated that the

acronym MNR2 is used, making this name unclear. The Examiner stated that MNR2 is not defined such that one skilled in the art could recognize the limitations of the claim. The Examiner directed applicants to see also the dependent claims.

In response, applicants respectfully traverse the Examiner's rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claim 27. Newly amended claim 27 now recites "An isolated homeobox motor neuron restricted pattern protein designated MNR2 comprising consecutive amino acids having the amino acid sequence set forth in SEQ ID NO:1 . . . ." Applicants contend that this amendment obviates the above rejection of claim 27 and the claims which depend therefrom. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim 45

The Examiner stated that in claim 45, it is not clear how only a single somatic motor neuron will be affected by the systemic administration of MNR2. Also, the Examiner questioned what the somatic motor neuron is being differentiated into.

In response, applicants respectfully traverse the Examiner's rejection. Applicants note that claim 45 does not recite a specific method of administration. Nor do applicants limit administration of MNR2 to systemic administration as the Examiner asserts. Instead, on page 53, lines 3-13 of the subject specification applicants teach that the protein may be

administered locally, i.e. intramuscularly, intrathecally, epidurally, intraperitoneally or subcutaneously, as a liquid pharmaceutical composition. Furthermore, applicants also note that the method of administering MNR2 will vary with the particular type of pharmaceutical composition comprising the MNR2 protein and can be easily determined by those of skill in the art (see page 53, line 33 - page 54, line 7 of the subject specification). One of skill in the art may easily determine the mode of administering the MNR2 protein so as to cause the differentiation of a single motor neuron.

In addition, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claim 45. Newly amended claim 45 now recites "A method of inducing differentiation of a neural progenitor cell into a somatic motor neuron in a subject comprising administering to the subject the protein of claim 27 in an amount effective to induce differentiation of the neural progenitor cell into a somatic motor neuron, so as to thereby induce differentiation of the neural progenitor cell into a somatic motor neuron in the subject."

Applicants contend that these remarks obviate the above rejection of claim 45. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claims 49, 50, 52 and 60

The Examiner stated that in claim 49, it is not clear what abnormality is associated with a lack of one or more normally functioning motor neurons. Also, the Examiner stated that the phrase "effective to a generate" is awkward. The Examiner directed applicants to see also claims 50 and 52.

In response, applicants respectfully traverse the Examiner's rejection. On page 72, lines 14-16 applicants set forth that "a 'normally functioning motor neuron' is a motor neuron that can control muscle contraction and respond to sensory input." Therefore, an "abnormality associated with a lack of one or more normally functioning motor neurons" would include any abnormality wherein the motor neuron can no longer control muscle contraction or respond to sensory input normally. For example, any trauma to a motor neuron or genetic defect of a motor neuron that would cause the motor neuron to function abnormally would be encompassed by this claim. Applicants contend that whether such an abnormality exists in a subject would be easily determinable by one of skill in the art.

In addition, with respect to the allegedly awkward language of claims 49, 50 and 52, without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application, applicants have hereinabove amended these claims to remove such language.

The Examiner stated that claim 50 is indefinite because the neurodegenerative disease is not stated. The Examiner stated

that claims 52 and 60 also lack specific diseases to be treated.

In response, applicants respectfully traverse. With respect to claim 50, applicants have set forth on page 73, lines 7-11 of the subject specification two examples of neurodegenerative diseases, e.g. spinal muscular atrophy and amyotrophic lateral sclerosis (Lou Gehrig's Disease). Therefore, one of skill in the art would know what is meant by a neurodegenerative disease. Accordingly, applicants contend that claim 50 is not indefinite to those of skill in the art.

In addition, with respect to claim 52, applicants note that what constitutes an "acute nervous system injury" is well known by those of skill in the art. For example, applicants attach hereto as **Exhibit C** an article entitled "Acute Nerve Injury" which sets forth on page 1 the various synonyms for an "acute nerve injury." Applicants also attach hereto as **Exhibit D** Notice NS-01-004 published on December 20, 2000 by the National Institute of Neurological Disorders And Stroke (NINDS) which discusses "acute spinal cord injuries". Therefore, at the time the subject application was filed the meaning of an "acute nervous system injury" was well known by those of skill in the art. Accordingly, applicants contend that claim 52 is not indefinite to those of skill in the art.

Finally, with respect to claim 60, applicants note that what constitutes a "neuromuscular disease" is well known by those of skill in the art. For example, applicants attach hereto as **Exhibit E** a copy of the webpage from The Department of

Neurology at Baylor College of Medicine which sets forth the definition of a neuromuscular disorder/disease and a listing of specific examples (see also **Exhibit F**, copy of webpage from The Department of Neurology at Wake Forest University Baptist Medical Center). Therefore, at the time the subject application was filed the meaning of an "neuromuscular disease" was well known by those of skill in the art. Accordingly, applicants contend that claim 60 is not indefinite to those of skill in the art.

Applicants contend that these remarks obviate the above rejections. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, First Paragraph

Written Description

The Examiner rejected claims 27, 127, and 128 under 25 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner stated that the specification does not provide written description of mouse, rat, or human MNR2 protein.

In response, applicants respectfully traverse the Examiner's rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite

prosecution of the subject application have hereinabove amended claim 128. Newly amended claim 128 no longer recites "mouse, rat or human" with respect to the MNR2 protein of claim 127. Applicants contend that this amendment obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Enablement

The Examiner stated that claims 27, 45, 48, 49, 50, 52, 60, 127, and 128 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for MNR2 comprising SEQ ID NO: 1, does not reasonably provide enablement for all MNR2. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Examiner stated that in *Ex parte Forman* (230 USPQ 546) the Board considered the issue of enablement in molecular biology. The Examiner stated that the Board held that the following factors should be considered to determine whether the claimed invention would require of the skilled artisan undue experimentation: (1) quantity of experimentation necessary: The Examiner stated that it would require undue experimentation to acquire all MNR2 across all species, to the scope of the claims; (2) amount of direction or guidance presented: The Examiner stated that at page 45 and 47+ of the specification, routineers in the field are invited to find for themselves, the scope of the MNR2 proteins as claimed, via

nucleic acid probes, or antibody assays; (3) presence or absence of working examples: The Examiner stated that there are none; (4) the nature of the invention; (5) state of the prior art; (6) relative skill of those in the art: The Examiner stated that the invention is highly technical and the MNR2 protein is not recognized in the prior art. The Examiner stated that those working in the art are highly skilled; (7) predictability or unpredictability of the art: The Examiner stated that finding a protein that is involved in the differentiation of neurons is highly unpredictable; and (8) breadth of the claims: The Examiner stated that the claims are very broad. The Examiner stated that for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention.

In response, applicants respectfully traverse the Examiner's rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claim 27. Newly amended claim 27 now recites "An isolated homeobox motor neuron restricted pattern protein designated MNR2 comprising consecutive amino acids having the amino acid sequence set forth in SEQ ID NO:1 or a fragment having the biological activity thereof." Applicants contend that this amendment obviates the above rejection of claim 27 and claims 45, 48, 49, 50, 52, 60, 127, and 128 which depend therefrom. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner rejected claims 45, 49, 50, 52 and 60 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner stated that these claims are drawn to methods of treating neurological diseases/injuries by administering the MNR2 protein systemically to a subject, thus causing differentiation of neuronal precursor cells. The Examiner stated that these methods are not art-recognized such that there could be a nexus between other prior art proteins and the treatment of neurological disease/injury and MNR2.

The Examiner stated that in *Ex parte Forman* (230 USPQ 546) the Board considered the issue of enablement in molecular biology. The Examiner stated that the Board held that the following factors should be considered to determine whether the claimed invention would require of the skilled artisan undue experimentation: (1) quantity of experimentation necessary: The Examiner stated that it would require undue experimentation to determine how one would treat diseases/injuries that are not known to be routinely treatable with a new protein that is involved with neuronal cell differentiation; (2) amount of direction or guidance presented: The Examiner stated that page 50+ provides a generic discussion of methods of treatment using protein, and these methods are not specific to neural abnormalities; (3) presence or absence of working examples: The Examiner stated

that there are none; (4) nature of the invention; (5) state of the art; (6) relative skill of those in the art: The Examiner stated that the invention is highly technical and the MNR2 protein is not recognized in the prior art. The Examiner stated that those working in the art are highly skilled; (7) predictability or unpredictability of the art: The Examiner stated that finding a protein that is involved in the differentiation of neurons is highly unpredictable - using the protein to differentiate neuronal cells *in vivo* is highly unpredictable; and (8) breadth of the claims: The Examiner stated that the claims are very broad. The Examiner stated that for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention.

In response, applicants respectfully traverse the Examiner's rejection. Applicants note that claims 45, 49, 50, 52 and 60 do not recite a specific method of administration. Nor do applicants limit administration of MNR2 to systemic administration as the Examiner asserts. Instead, on page 53, lines 3-13 of the subject specification applicants teach that the protein may be administered locally, i.e. intramuscularly, intrathecally, epidurally, intraperitoneally or subcutaneously, as a liquid pharmaceutical composition. Furthermore, applicants also note that the method of administering MNR2 will vary with the particular type of pharmaceutical composition comprising the MNR2 protein which can be easily determined by those of skill in the art (see page 53, line 33 - page 54, line 7 of the subject specification). Applicants maintain that one of skill in the

art may easily determine the mode of administering the MNR2 protein so as to cause the differentiation of a single motor neuron.

Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim Objection

The Examiner objected to claim 125 as being dependent upon a rejected base claim. However, the Examiner stated that claim 125 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

In response, applicants respectfully traverse the Examiner's above objection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claim 125 without prejudice or disclaimer to their right to pursue this claim in a later-filed application. Applicants contend that this amendment obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following references which are listed on the PTO-1449 form attached hereto as **Exhibit A.** Copies of references 1-7, 9-10, 13, 16, 18, 20, 27-30, 33, 36-37, 40, 43, 45-50, 55-56, 58, 60, 63-69, 73, 78, 82, 87, 90-99, 105, 109, 111-112 and 114 are attached hereto as **Exhibits 1-58** respectively.

1. U.S. Patent No. 6,387,656 B1, issued May 14, 2002 to Jessell et al. **(Exhibit 1)**;

2. PCT International Application No. PCT/US99/22517, filed September 29, 1999, International Publication No. WO00/18884, published April 6, 2000 on behalf of The Trustees of Columbia University in the City of New York **(Exhibit 2)**;

3. U.S. Serial No. 10/095,932, filed March 11, 2002 on behalf of Thomas M. Jessell et al. **(Exhibit 3)**;

4. Ahlgren, U. et al. (1996) "The Morphogenesis of the Pancreatic Mesenchyme Is Uncoupled from That of the Pancreatic Epithelium in IPF1/PDX1-deficient Mice", *Development* 122:1409-1416 **(Exhibit 4)**;

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The subject application is a continuation of PCT International Application No. PCT/US99/22517, filed September 29, 1999, designating the United States of America, which is a continuation-in-part of U.S. Serial No. 09/162,524, filed September 29, 1998, now U.S. Patent No. 6,387,656 B1, issued May 14, 2002, a copy of which patent is attached hereto as **Exhibit 1**.

Above listed references 8, 12, 14-15, 19, 21-22, 26, 31-32, 34-35, 38, 41-42, 44, 51-54, 57, 59, 61-62, 70-72, 74-75, 79-81, 83-86, 88-89, 100-103, 106-108, 110 and 113 were submitted to and considered by the United States Patent and Trademark Office in an Information Disclosure Statement filed on August 20, 1999 in connection with U.S. Serial No. 09/162,524, filed September 29, 1998, now U.S. Patent No. 6,387,656 B1, issued

May 14, 2002. Above listed references 17, and 23-25 were cited by the United States Patent and Trademark Office in an Office Action dated October 22, 1999 in connection with U.S. Serial No. 09/162,524, filed September 29, 1998, now U.S. Patent No. 6,387,656 B1, issued May 14, 2002. Above listed reference 76 was cited by the United States Patent and Trademark Office in an Office Action dated July 20, 2000 in connection with U.S. Serial No. 09/162,524, filed September 29, 1998, now U.S. Patent No. 6,387,656 B1, issued May 14, 2002. Above listed reference 77 was cited by the United States Patent and Trademark Office in an Office Action dated April 11, 2001 in connection with U.S. Serial No. 09/162,524, filed September 29, 1998, now U.S. Patent No. 6,387,656 B1, issued May 14, 2002. Accordingly, under 37 C.F.R. §1.98(d) copies of these references are not required to be provided to the United States Patent and Trademark Office, since they were previously submitted to or cited by the United States Patent and Trademark Office in an application relied upon for an earlier filing date under 35 U.S.C. §120.

PCT International Application No. PCT/US99/22517, filed September 29, 1999, is a foreign counterpart application of the subject application. A copy of PCT International Application No. PCT/US99/22517 is attached hereto as **Exhibit 2**. A Search Report was issued on January 25, 2000 in connection with PCT International Application No. PCT/US99/22517, filed September 29, 1999. A copy of the Search Report is attached hereto as **Exhibit B**. Above listed references 11, 25, 39, 86 and 104 were cited in the Search Report. Above listed reference 86 was submitted to and

considered by the United States Patent and Trademark Office in an Information Disclosure Statement filed on August 20, 1999 in connection with U.S. Serial No. 09/162,524, filed September 29, 1998. Above listed reference 25 was cited by the United States Patent and Trademark Office in an Office Action dated October 22, 1999 in connection with U.S. Serial No. 09/162,524, filed September 29, 1998. Above listed references 11 and 104 were submitted to and considered by the United States Patent and Trademark Office in a Supplemental Information Disclosure Statement filed on April 24, 2000 in connection with U.S. Serial No. 09/162,524, filed September 29, 1998. Above listed reference 39 was cited by the United States Patent and Trademark Office in an Office Action dated April 11, 2001 in connection with U.S. Serial No. 09/162,524, filed September 29, 1998. Accordingly, under 37 C.F.R. §1.98(d) copies of these references are not required to be provided to the United States Patent and Trademark Office, since they were previously submitted to or cited by the United States Patent and Trademark Office in an application relied upon for an earlier filing date under 35 U.S.C. §120.

U.S. Serial No. 10/095,932, filed March 11, 2002 is a divisional of U.S. Serial No. 09/162,524, filed September 29, 1998, now U.S. Patent No. 6,387,656 B1, issued May 14, 2002. A copy of U.S. Serial No. 10/095,932, including a Preliminary Amendment which applicants submitted to the U.S. Patent Office on March 11, 2002 which includes the currently pending claims, is attached hereto as **Exhibit 3**.

Pursuant to 37 C.F.R. §1.97(c)(2), a $180.00 fee is required in connection with the filing of this Information Disclosure Statement and a check which includes this amount is enclosed.

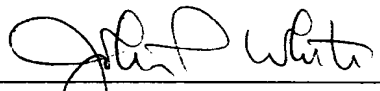
Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection and objection and earnestly solicit allowance of the pending claims, i.e. claims 27, 45, 48, 49, 50, 52, 60 and 126-128.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $180.00 fee for submitting an Information Disclosure Statement under 37 C.F.R. §1.97(c)(2), is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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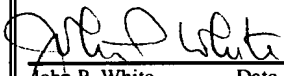
I hereby certify that this correspondence is being deposited this date with the U.S. postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



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John P. White Date
Reg. No. 28,678

Form PTO-1449 U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 0575/57477-A-PCT-US	Serial No. 09/820,598
INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Applicants: Thomas M. Jessell et al.	
	Filing Date March 29, 2001	Group 1653

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Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate
		6,387,656	05/14/02	Jessell et al. **(Exhibit 1)**			

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							Yes	No
	WO	00188284	04/06/00	PCT **(Exhibit 2)**				

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		Roztocil, T. et al. (1997) "NeuroM, a Neural Helix-loop-helix Transcription Factor, Defines a New Transition Stage in Neurogenesis", *Development* 124:3263-3272;
		Ruiz i Altaba et al. (1993) "Ectopic Neural Expression of a Floor Plate Marker in Frog Embryos Injected with the Midline Transcription Factor Pintallavis", *Proc. Natl. Acad. Sci. USA* 90:8268-8272;
		Ruiz i Altaba et al. (1995) "Restrictions to Floor Plate Induction by Hedgehog and Winged-helix Genes in the Neural Tube of Frog Embryos", *Mol. Cell Neurosci.* 6:106-121;
		Saha, M.S. et al. (1997) "Dorsal-Ventral Patterning During Neural Induction in Xenopus: Assessment of Spinal Cord Regionalization with xHB9, a Marker for the Motor Neuron Region", *Dev. Biol.* 187:209-223;
		Sander M. et al. (1997) "Genetic Analysis Reveals that PAX6 is Required for Normal Transcription of Pancreatic Hormone Genes and Islet Development", *Genes Dev.* 11:1662-1673 **(Exhibit 43)**;
		Sasaki, H. et al. (1994) "HNF-3 Beta as a Regulator of Floor Plate Development", *Cell* 76:103-115;
		Schaeren-Wiemers, N. et al. (1993) "A Single Protocol to Detect Transcripts of Various Types and Expression Levels in Neural Tissue and Cultured Cells: in Situ Hybridization Using Digoxigenin-labeled cRNA Probes", *Histochemistry* 100:431-440;
		Sharma, A. et al. (1995) "The Reduction of Insulin Gene Transcription in HIT-T15 Beta Cells Chronically Exposed to High Glucose Concentration Is Associated with the Loss of RIPE3b1 and STF-1 Transcription Factor Expression", *Mol. Endocrinol.* 9:1127-1134 **(Exhibit 44)**;

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 0575/57477-A-PCT-US	Serial No. 09/820,598
INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Applicants: Thomas M. Jessell et al.	
	Filing Date March 29, 2001	Group 1653

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Sharma, K. et al. (1998) "LIM Homeodomain Factors Lhx3 and Lhx4 Assign Subtype Identities for Motor Neurons", *Cell* 95:817-828 **(Exhibit 45)**;
		Slack, J.M.W. (1995) "Developmental Biology of the Pancreas", *Development* 121:1569-1580 **(Exhibit 46)**;
		Sockanathan, S. et al. (1998) "Motor Neuron- Derived Retinoid Signaling Specifies the Subtype Identity of Spinal Motor Neurons", *Cell* 94:503-514 **(Exhibit 47)**;
		Sosa-Pineda, B. et al. (1997) "The *Pax4* Gene Is Essential for Differentiation of Insulin-producing Beta Cells in the Mammalian Pancreas", *Nature* 386:399-402 **(Exhibit 48)**;
		Spooner, B.S. et al. (1970) "The Development of the Dorsal and Ventral Mammalian Pancreas In Vivo and In Vitro", *J. Cell Biol.* 47:235-246 **(Exhibit 49)**;
		Stoffers, D.A. et al. (1997) "Early-onset Type-II Diabetes Mellitus (MODY4) Linked to *IPF1*", *Nature Genet.* 17:138-139 **(Exhibit 50)**;
		Stoffers, D.A. et al. (1997) "Pancreatic Agenesis Attributable to a Single Nucleotide Deletion in the Human *IPF1* Gene Coding Sequence", *Nature Genet.* 15:106-110 **(Exhibit 51)**;
		St-Onge, L. et al. (1997) "*Pax6* Is Required for Differentiation of Glucagon-producing Alpha-cells in Mouse Pancreas", *Nature* 387:406-409 **(Exhibit 52)**;
		Sussel, L. et al. (1998) "Mice Lacking the Homeodomain Transcription Factor Nkx2.2 Have Diabetes Due to Arrested Differentiation of Pancreatic Beta Cells", *Development* 125:2213-2221 **(Exhibit 53)**;
		Tanabe, Y. et al. (1995) "Induction of Motor Neurons by Sonic Hedgehog Is Independent of Floor Plate Differentiation", *Curr. Biol.* 5:651-658;

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 0575/57477-A-PCT-US	Serial No. 09/820,598
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	Filing Date March 29, 2001	Group 1653

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Tanabe, Y. et al. (1996) "Diversity and Pattern in the Developing Spinal Cord", *Science* 274:1115-1123;
		Tanabe, Y. et al. (1998) "Specification of Motor Neuron Identity by the MNR2 Homeodomain Protein", *Cell* 95:67-80;
		Tanaka, H. et al. (1984) "Developmental Changes in Unique Cell Surface Antigens of Chick Embryo Spinal Motor Neurons and Ganglion Cells", *Dev. Biol.* 106:26-37;
		Thaler et al. (1999) "Active Suppression of Interneuron Programs with Developing Motor Neurons Revealed by Analysis of Homeodomain Factor HB9", *Neuron* 23:675-687;
		Tosney, K.W. et al. (1985) "Development of the Major Pathways for Neurite Outgrowth in the Chick Hindlimb", *Dev. Biol.* 109:193-214 **(Exhibit 54)**;
		Tsuchida, T. (1994) "Topographic Organization of Embryonic Motor Neurons Defined by Expression of LIM Homeobox Genes", *Cell* 79:957-70;
		Varela-Echavarría, A. et al. (1996) "Differential Expression of LIM Homeobox Genes among Motor Neuron Subpopulations in the Developing Chick Brain Stem", *Mol. Cell. Neurosci.* 8:242-257;
		Weintraub, H. (1993) "The MyoD Family and Myogenesis: Redundancy, Networks, and Thresholds", *Cell* 75:1241-1244;
		Wessells, N.K. &. Cohen, J.H. (1967) "Early Pancreas Organogenesis: Morphogenesis, Tissue Interactions, and Mass Effects", *Dev. Biology* 15:237-270 **(Exhibit 55)**;
		Westendorf, J.M. et al. (1994) "Cloning of cDNAs for M-Phase Phosphoproteins Recognized by the MPM2 Monoclonal Antibody and Determination of the Phosphorylated Epitope", *Proc. Natl. Acad. Sci. USA* 91:714-718;
		Wetts, R. et al. (1995) "Transient and Continuous Expression of NADPH Diaphorase in Different Neuronal Populations of Developing Rat Spinal Cord", *Dev. Dyn.* 202:215-228 **(Exhibit 56)**;

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Form PTO-1449 U.S. Department of Commerce Patent and Trademark Office	Atty. Docket No. 0575/57477-A-PCT-US	Serial No. 09/820,598
INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Applicants: Thomas M. Jessell et al.	
	Filing Date March 29, 2001	Group 1653

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Wildling, R. et al. (1993) "Agenesis of the Dorsal Pancreas in a Woman with Diabetes Mellitus and in Both of Her Sons", *Gastroenterology* 104:1182-1186 **(Exhibit 57)**;
		Yamada, T. et al. (1993) "Control of Cell Pattern in the Neural Tube: Motor Neuron Induction of Diffusible Factors From Notochord and Floor Plate", *Cell* 73:673-686; and
		Zhao, D. et al. (1996) "Molecular Identification of a Major Retinoic-Acid-Synthesizing Enzyme, a Retinaldehyde-Specific Dehydrogenase", *Eur. J. Biochem.* 240:15-22 **(Exhibit 58)**.

EXAMINER	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: JOHN P. WHITE
COOPER & DUNHAM LLP
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of Mailing *(day/month/year)* 25 JAN 2000
Applicant's or agent's file reference 57477-A-PCT	**FOR FURTHER ACTION** **See paragraphs 1 and 4 below**
International application No. PCT/US99/22517	International filing date *(day/month/year)* 29 SEPTEMBER 1999
Applicant THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK	

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer RICHARD SCHNIZER
Facsimile No. (703) 305-3230	Telephone No. (703)

Form PCT/ISA/220 (January 1994)*

Applicant: Thomas M. Jessel et al.
U.S. Serial No.: 09/820,598
Filed: March 29, 2001
Exhibit B

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 57477-A-PCT	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US99/22517	International filing date *(day/month/year)* 29 SEPTEMBER 1999	(Earliest) Priority Date *(day/month/year)* 29 SEPTEMBER 1998
Applicant THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (See Box I).

2. [X] **Unity of invention is lacking** (See Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [X] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] transcribed by this Authority.

4. With regard to the **title**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   - [ ] the text is approved as submitted by the applicant.
   - [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22517

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 13, 70, 73, 77, and 90-97
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The abstract cannot exceed 200 words, PCT Rule 8.1(b).

NEW ABSTRACT

This invention provides isolated nucleic acids encoding a motor neuron restricted MNR2 protein, and a homeobox HB9 protein. Also provided are purified MNR2 and HB9 proteins, antibodies recognizing these proteins, transgenic animals expressing these proteins, and functionally equivalent analogs of these proteins. Finally, methods are disclosed for inducing differentiation of somatic motor neurons, and for treating diseases related to a lack of normally functioning motor neurons, neurodegenerative diseases, acute nervous system injury, and neuromuscular disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22517

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/69.1, 252.3, 320.1, 325, 419; 536/23.5, 24.31, 24.5; 530/350, 387.1; 800/8

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: MEDLINE CAPLUS BIOSIS EMBASE BIOTECHDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X ---- A, X	TANABE et al. Specification of motor neuron identity by the MNR2 homeodomain protein. Cell. October 1998, Vol. 95, pages 67-80, entire document.	1-7,9,14-17 27-33, 34-40, 44, 48 ---------- 8, 10-13, 41-43, 45-47, 49-60
X -- Y	Database Tumor Gene Index. Accession No. AI560820. NCI-CGAP. National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index. Entire document, especially bases 50-129. June 1998.	18-23 --------- 24-26

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
08 NOVEMBER 1999	25 JAN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RICHARD SCHNIZER Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22517

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y -- A	HARRISON et al. A novel human homeobox gene distantly related to *proboscipedia* is expressed in lymphoid and pancreatic tissues. Journal of Biological Chemistry. August 1994, Vol. 269, No. 31, pages 19968-19975, entire document, especially materials and methods.	61-68, 71, 74-76, 78-89 --- 101, 102, 108 --- 69, 98-100, 103, 104-107, 109-124
X -- Y -- A	DEGUCHI et al. Nucleotide sequence of a novel diverged human homeobox gene encodes a DNA binding protein. Nucleic Acids Research. 1991, Vol. 19, No. 13, page 3742, entire document.	61-64, 68, 71,72,74, 75,78-83 --- 84-89,101,102,104, 108 --- 76, 98-100,103,105-107, 109-124
X -- Y -- A	SAHA et al. Dorsal-ventral patterning during neural induction in *Xenopus*: Assessment of spinal cord regionalization with *xHB9*, a marker for the motor neuron region. Developmental Biology. July 1997, Vol. 187, pages 209-223, entire document.	61-68, 74, 75, 78-83 --- 84-86, 101, 102, 104, 108 --- 69, 76, 98-100, 103, 105-107, 109-124
A, P	ARBER et al. Requirement for the homeobox gene Hb9 in the consolidation of motor neuron identity. Neuron. August 1999. Vol. 23, No. 4, pages 659-674, entire document.	61-89, 98-124
A, P	THALER et al. Active suppression of interneuron programs with developing motor neurons revealed by analysis of homeodomain factor HB9. Neuron. August 1999, Vol 23, No. 4, pages 675-687, entire document.	61-89, 98-124

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22517

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

C12N 1/21, 15/00, 15/11, 15/63, 15/85, 15/86; C07H 21/02, 21/04; C07K 14/00, 16/00; A01K 67/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/69.1, 252.3, 320.1, 325, 419; 536/23.5, 24.31, 24.5; 530/350, 387.1; 800/8

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE
2. Where no meaningful search could be carried out, specifically:

Claim 13 is drawn to the nucleotide sequence of SEQ ID No. 1. SEQ ID No.1 is not a nucleotide sequence, it is a chick MNR2 amino acid sequence. Claims 70, 73, 77, and 90-97 recite amino acid or nucleotide sequences of an HB9 protein or gene as encoded by SEQ ID No.1. SEQ ID No.1 is not an HB9 amino acid or nucleotide sequence, it is a chick MNR2 amino acid sequence.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I, claim(s)1-12, 14-26, and 44, and drawn to MNR2 nucleic acids, vectors and host cells comprising them, and a first method of using the nucleic acids to produce an MNR2 protein.
Group II, claim(s) 27-33, 48-55 and 60, drawn to a purified MNR2 protein, and methods of using it.
Group III, claim(s) 34-37, drawn to anti-MNR2 antibodies.
Group IV, claim(s) 41 and 42, drawn to a nonhuman transgenic animal comprising an MNR2 transgene and a method of using it.
Group V, claim(s) 56 and 57, drawn to a second method of using MNR2 nucleic acids, to diagnose neurological disorders.
Group VI, claim(s) 58 and 59, drawn to unidentified compounds of unknown structure which are functional analogs of MNR2.
Group VII, claim(s) 61-69, 71, 72, 74-76, 78-86 and 104, drawn to HB9 nucleic acids, vectors and host cells comprising them, and a first method of using them to produce HB9 protein.
Group VIII, claim(s) 87-89, 108, and 120-124, drawn to a purified HB9 protein and methods of using it.
Group IX, claim(s) 101-102, drawn to a transgenic animal comprising an HB9 transgene and a method of using it.
Group X, claim(s) 116, and 117, drawn to a second method of using HB9 nucleotides, to diagnose neurological disorders.
Group XI, claim(s) 118 and 119, drawn to unidentified compounds of unknown structure which are functional analogs of HB9.

The inventions listed as Groups I-XI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group I is drawn to a group of products, specifically all MNR2 nucleic acids. Groups II-IV, VI-IX and XI are drawn to independent products, and group V is drawn to a second method of using the invention of group I. 37 C.F.R. 1.475(b) does not provide for multiple independent products, and only provides for a first method of using the product. Group X is drawn to a method of using a product which is independent of the product of group I.

Therefore the claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single general inventive concept.

Acute Nerve Injury

Last Updated: June 5, 2002

Synonyms and related keywords: neurosurgery, nerve injury, nerve repair, neurapraxia, axonotmesis, neurotmesis, fractures, fracture-dislocations, mechanical injury, crush injury, percussion injury, laceration injury, peripheral nerve damage, nerve damage, blunt trauma, penetrating trauma, stretch injury, high-velocity trauma

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Editor(s): **Duc Hoang Duong, MD**, Director of Neuroscience Physician Assistant Program, Associate Professor, Departments of Neurological Surgery and Neuroscience, Epilepsy Center, Charles R Drew University; **Francisco Talavera, PharmD, PhD**, Senior Pharmacy Editor, Pharmacy, eMedicine; **Allen R Wyler, MD**, Executive Medical Director, Department of Neurosurgery, Division of Epilepsy, Vertis Neuroscience; **Herbert H Engelhard, MD, PhD**, Chief, Division of Neuro-Oncology, Associate Professor, Departments of Neurosurgery and Molecular Genetics, University of Illinois at Chicago; and **Michael Dogali, MD, CM**, Professor, Department of Neurological Surgery, University of Southern California School of Medicine

INTRODUCTION

Complications Outcome And Prognosis Future And Controversies Bibliography

History of the Procedure: Reports of acute nerve injury can be traced to 3500 years ago. In the well-known biblical story, Jacob suffered a sciatic nerve injury with a traumatic hip dislocation during his battle with the angel (Genesis 32:25-33) (Cornwall, 2000). However, no specific technique to repair peripheral nerve damage was described until the 16th century.

Gabriele Ferrara (1543-1627) was a pioneer of peripheral nerve surgery. He was the first surgeon to describe the technique of suturing the stumps of a transected nerve. His technique included precise identification of the nerve stumps; gentle traction; applying alcohol to disinfect the suture needle and suture thread using a mixture of red wine, rosemary, and roses; and gently sewing the retracted stumps together without damaging them. Oils were then applied, and the patient was confined to bed with the limb immobilized to prevent damaging the suture. This procedure, consisting of disinfection, appropriate identification of nerve stumps, correct suturing technique, and limb immobilization, closely resembles the surgical protocol of the 21st century (Artico, 1996).

Before World War II (WW II), nerves were believed to be cords and consequently received little attention. Nerve repair consisted of simple reapproximation and suturing. During World War I, nerve injuries were repaired under tension and risked disruption after repair because of extensive soft tissue injuries and significant infections. During WW II, reoccurrence of these war injuries influenced experimental studies to further investigate the anatomy of the peripheral nerve. Poor outcomes of peripheral nerve damage repair were recognized to be the result of failed axonal regeneration at the site of the repair (Colohan, 1996). An important quality of the peripheral nervous system, as compared to the central nervous system, is its remarkable ability to recover after an injury through remyelination and regeneration of the axon (Grant, 1999).

Technological advances in neurosurgical instrumentation and diagnostic imaging have led to great results in the repair of acute nerve injury (Artico, 1996). However, in recent years, reconstruction of nerve injuries has made little improvement in functional outcome after repair of peripheral nerves (Trumble, 2000).

Problem:

Definition of nerve injury

Classification of nerve injury is based on the damage sustained by the nerve components, nerve functionality, and the ability for spontaneous recovery (Grant, 1999; Greenfield, 1997; Ristic, 2000). Seddon (1943)

published his classification of nerve injuries, and Sunderland (1951) expanded this grading system (Ristic, 2000). The significance of Seddon's 3-grade classification system is its clinical relevance in predicting functional outcome and formulating an appropriate treatment plan (Grant, 1999).

The mildest grade is called neurapraxia. Neurapraxia is a reduction or complete block of conduction across a segment of a nerve with axonal continuity conserved (Colohan, 1996; Grant, 1999; Trumble, 2000). More specifically, it is dysfunction and/or paralysis without loss of nerve sheath continuity and peripheral wallerian degeneration (Ristic, 2000; Schwartz, 1999). Nerve conduction is preserved both proximal and distal to the lesion but not across the lesion (Grant, 1999). A person's foot "falling asleep" after his legs have been crossed is an example of a functional loss without abnormal change (Greenfield, 1997).

Axonotmesis is a more severe grade of nerve injury compared to neurapraxia. Axonotmesis is a result of damage to the axons with preservation of the neural connective tissue sheath (endoneurium), epineurium, Schwann cell tubes, and other supporting structures (Colohan, 1996; Trumble, 2000; Grant, 1999). Thus, the internal architecture is relatively preserved (Schwartz, 1999). This can guide proximal axonal regeneration to reinnervate distal target organs (Colohan, 1996; Greenfield, 1997). Distal wallerian degeneration occurs in axonotmesis (Ristic, 2000).

Neurotmesis is the most severe grade of peripheral nerve injury. It occurs when the axon, myelin, and connective tissue components are damaged and disrupted or transected (Greenfield, 1997; Ristic, 2000; Schwartz, 1999). Recovery through axonal regeneration cannot occur. This grade of injury includes nerve lesions in which external continuity is preserved but intraneural fibrosis occurs and blocks axonal regeneration (Grant, 1999; Schwartz, 1999).

Sunderland (1951) categorized nerve injuries into 5 grades. Grades I and II correspond to Seddon's neuropraxic and axonotmetic grades of injury. Sunderland further divided Seddon's category of neurotmesis injuries into grades III, IV, and V based on the extent of damage to the axonal supporting structures (Grant, 1999).

In grade III injuries, axon continuity is disrupted by loss of endoneurial tubes (the neurolemmal sheaths) but the perineurium is preserved. Thus, when the axons regenerate, they may enter an incorrect nerve sheath, resulting in abnormal regeneration (Grant, 1999; Ristic, 2000). Accompanying the loss of the nerve sheath is intraneural scarring, which further obstructs axonal regrowth through the site of injury (Colohan, 1996). In grade IV injuries, nerve fasciculi (ie, axon, endoneurium, perineurium) are damaged but nerve sheath continuity is

plexus. This results in a stretch injury. Traction injuries to the peripheral nerve trunk limb girdle plexuses or to spinal nerve roots can occur in a number of ways. Injuries to the lumbosacral plexus or to the lumbosacral roots commonly are associated with fractures of the pelvis. Displacement of fractures and joint dislocations can result in stretch injury to peripheral nerves. Stretch injury to peripheral nerves may occur during operative or other surgical procedures (Adams, 1992). Stretching of the nerve around the radial neck during a closed reduction is an example of procedural etiology for stretch injury (Ristic, 2000).

A sixth mechanism of injury is high-velocity trauma caused by motor vehicle accidents and gunshot wounds. Gunshot wounds can cause direct nerve damage by avulsing soft tissue, causing severe tissue destruction (Greenfield, 1997; Adams, 1992). Open and closed fractures of the radius, gunshot wounds, and contusions also cause traumatic posterior interosseous nerve injury around the proximal forearm (Ristic, 2000). These types of fractures can occur in motor vehicle accidents. Nerves not directly damaged can be affected secondary to rapid tissue expansion in the track of a missile wound (Adams, 1992).

A seventh mechanism of injury is cold injury. Frostbite leads to necrosis of all involved tissues, including the peripheral nerves. Several hours of nonfreezing exposure with a temperature above -2.5° C and below 10°C damages peripheral nerves because they are more vulnerable than the surrounding tissue (Adams, 1992).

Other contributing factors explain the statistical probability in the distribution of acute nerve injury. The anatomical relationship between the peripheral nerves and surrounding tissues causes certain nerves to be vulnerable to injury. The peroneal division of the sciatic nerve is affected more commonly in traumatic hip dislocations because the peroneal division is tethered at the fibular neck and at the sciatic notch and the tibial division is tethered only at the sciatic notch. This difference allows the tibial division a greater length over which to dissipate stresses. The funiculi of the peroneal division are fewer, larger, and protected by less connective tissue than those in the tibial division. Therefore, at the time of injury, a dislocated femoral head or displaced acetabular fragments can directly injure the sciatic nerve.

Operative findings establish that in traumatic hip injuries, the sciatic nerve can be compromised in a number of ways. These include direct compression of the sciatic nerve by the dislocated femoral head, compression by acetabular fragments, laceration or puncture by the acetabular fragments, or entrapment in the acetabular fragments (Cornwall, 2000).

Anatomic positions of the radial, median, and ulnar nerves, including

their branches, predispose them to injury with specific types of fractures. Examples include radial nerve palsies with a Holstein-Lewis distal one third humeral shaft fracture, posterior interosseous nerve injury with a Monteggia fracture-dislocation, ulnar nerve and/or anterior interosseous nerve injuries with elbow dislocations, median nerve and/or radial nerve injuries with supracondylar and medial epicondyle fracture in children, and ulnar nerve injury at the cubital tunnel (Ristic, 2000). Because of the construction of the human shoulder, a direct blow to the anterolateral deltoid muscle can damage the axillary nerve as it travels through the deep subfascial surface and then through the deltoid muscle. A glenohumeral dislocation, a proximal humerus fracture, or a direct blow to the deltoid muscle is the usual mechanism of injury to the axillary nerve (Perlmutter, 1999).

Injury to nerves also can occur from physiologic healing processes. For example, the sciatic nerve can be compressed from scar formation and massive heterotopic ossification after a hip trauma (Cornwall, 2000). After elbow trauma, scarring can jeopardize the normal gliding of the ulnar nerve in the elbow due to adherence to scar tissue, fracture callus, or heterotopic bone (Ristic, 2000).

Iatrogenic injury is another possible cause of acute nerve injury. Iatrogenic injury to the axillary nerve can occur in shoulder instability surgery. Here, the axillary nerve injury can be secondary to tension, suture compression, or iatrogenic laceration. Furthermore, in rotator cuff surgery, overzealous muscle splitting places the axillary nerve at risk for injury (Perlmutter, 1999). Posterior interosseous and median nerve injury can occur during elbow arthroscopy. Iatrogenic causes of traumatic posterior interosseous nerve injury around the proximal forearm have been documented (Ristic, 2000).

Pathophysiology: A stimulus to the human body elicits a response—appropriate or not. If the stimulus is injury to human tissue, the body's response is repair. Repair is a process of degeneration followed by regeneration. Wallerian degeneration occurs in peripheral nerves. It is a process by which the damaged segment of a nerve is phagocytosed, beginning at the first intact node of Ranvier. The Schwann cell tubes also are phagocytosed to prevent obstruction of the regenerating axon. Many different growth factors and cytokines affect this process of degeneration-regeneration. Nerve growth factor (NGF) has sparked much interest among researchers because of its ability to stimulate the wallerian degeneration and regeneration of sensory axons (Trumble, 2000).

Regeneration of a peripheral nerve occurs at rate of approximately 1 mm/d (Colohan, 1996; Grant, 1999; Greenfield, 1997; Ristic, 2000). In injuries that are more proximal, improvement may not be obvious for many months (Grant, 1999; Greenfield, 1997). For example, injuries to the midshaft level of the humerus may have to cross as many as 16

cm (>5 mo) before innervating the brachioradialis or wrist extensors (Ristic, 2000). Furthermore, in 1999, Perlmutter reported that because of the distance from the location of nerve injury to the deltoid muscle, signs of reinnervation of the axillary nerve would be observed 3-4 months after injury (Perlmutter, 1999).

At the beginning stage of regeneration, the proximal axon stump sprouts buds that comprise the nerve growth cone (Trumble, 2000). Axonal regeneration is guided towards the distal end of the nerve by a gradient of diffusible substances. This process is called neurotropism (Trumble, 2000). Due to the constricting effect of intraneural and extraneural scar tissue, axonal regrowth can be blocked at the site of the lesion (Greenfield, 1997). NGF affects the sensory regeneration but does not directly guide the regenerating axon. The axonal buds preferentially move toward neural tissue. However, they cannot differentiate between sensory or motor fascicles. The size of the distal fascicle appears to be the most significant factor in determining the target of the regenerating growth cone. Buds are more likely to find and attach to bigger fascicles (Trumble, 2000).

Misdirected axonal buds can result in abnormal nerve connections. Abnormal motor nerve innervations can cause jerky or awkward movement. Abnormal sensory nerve innervations can cause misperception of the location of touch or pain (Berkow, 1997). Motor endplates must be reinnervated within 18 months of trauma for function to be resumed (Schwartz, 1999). Prevention of motor endplate degradation is important to ensure motor functionality after regeneration is complete. Leupeptin inhibits calcium-activated neuronal protease (calpain), which disrupts the cytoskeletal elements of the motor endplates. This has been demonstrated in laboratory animals as a means of enhancing nerve regeneration by preventing digestion of the receptors in skeletal muscle (Trumble, 2000).

In general, most traumatic nontransecting nerve injuries result in increased nerve swelling and pressure caused by endoneurial edema within a noncompliant perineurium. Epineurial vascular stripping (ie, epineurectomy) in rat sciatic nerve, which interrupts the vasa nervorum, reproduces injuries that result in increased epineurial edema and pressure. This proves dependence of the subperineurial axonal population on an intact vasa nervorum. Studies have verified that ischemic reperfusion type injuries, similar to those observed in muscle and skin, are a significant cause of nerve injury (Santos, 2000).

Each of the mechanisms of injury that were mentioned earlier (see Etiology) causes specific damage to a nerve. The first mechanism of injury is mechanical injury, which can be described from analysis of animal experiments. In cats, studies with pressure cuffs demonstrate that focal demyelination causes the conduction block associated with this type of injury. Recovery occurs after remyelination of the axon.

Studies with baboons by Ochoa and Fowler and Gilliatt in 1972 illustrate that the demyelination is related to displacement of the axoplasm to either side from under the compressed region. Outward dislocation of myelin internodes and their invagination into adjacent myelin internodes accompanies the displacement. This process obliterates the node of Ranvier. The demyelination occurs at the displaced nodes and is recovered by remyelinating those myelin sheaths (Adams, 1992).

The second mechanism of injury, crush and percussion injury, has been the result of axonal interruption within the intact Schwann cell basal laminal tubes (Adams, 1992). In 2000, Santos discovered that crush injuries do not preserve the basal lamina of all myelinated axons due the presence of axonal sprouting and regeneration (Santos, 2000). After the injury, Schwann cells quickly invade the region, and regenerating axons cross within a few days. The surviving basal laminal tubes guide most of the regenerating axons to their former peripheral connections. This pathophysiology is borrowed from information obtained through animal studies because no information on percussion nerve injury is available from human studies. Experimental studies by Denny-Brown and Brenner in 1994 and Richardson and Thomas in 1979 have indicated a combination of segmental demyelination, periaxonal and intramyelinic edema, and axonal interruption of nerves damaged from compression injury (Adams, 1992).

In penetrating wounds, 2 possible injury outcomes exist, complete division and partial severance. With complete severance of the nerve, the severed nerve ends draw back because of their inherent elasticity (Adams, 1992). For this reason, transected stumps are tacked down firmly to surrounding tissues during surgery (Kim, 1996).

Both the proximal stump and distal stump have outgrowths. The outgrowth on the proximal stump consists of groups of intertwined regenerating axon buds and associated Schwann cells, each surrounded by a perineural sheath, resulting in a multicompartment arrangement. According to Thomas in 1966, the outgrowth on the distal stump consists of interlacing columns of Schwann cells, Büngner bands, and associated connective tissue of the endoneurial type (Adams, 1992). Büngner bands are longitudinal conduits formed by the proliferating Schwann cells, and axons can regenerate through them (Grant, 1999). In a penetrating wound with partial severance or following a nerve suture, the regenerating axons are able to reconnect with the distal portion and invade the Schwann cell Büngner bands (Adams, 1992).

The fourth injury, stretch injury, can cause a mild conduction block. Why stretch injury paralysis, which recovers within a couple of hours, occurs is uncertain. The time to recovery is too short for demyelination

and remyelination. According to Highet and Holmes in 1943, more severe degrees of stretch injury usually result in damage to a significant length of nerve with interruption of axons, disruption of neural connective tissues, and intraneural hemorrhage (Adams, 1992).

The fifth type of injury is lacerating injuries. This type of injury is localized within a few millimeters beyond the divided ends of the nerve (Colohan, 1996).

Cold injury is the sixth type of injury. Animal studies in nonfreezing cold injury, as described in Etiology, showed a focal conduction block and cessation of axonal transport in the acute stage, with early recovery of function. However, after a few days, axonal degeneration occurs, particularly of large myelinated fibers, as described by Basbaum in 1973 and Nukada, Pollock, and Allpress in 1981 (Adams, 1992). The mechanism of delayed degeneration is uncertain. The blood-nerve barrier has been demonstrated to become damaged, and extensive endoneurial edema occurs. This is a progressive process, probably due to the lack of endoneurial lymphatics. The greater vulnerability of the peripheral nerve can be explained if the raised intraneural pressure, secondary to edema, is the mechanism of fiber degeneration (Adams, 1992).

Clinical: Patients with acute peripheral nerve injury usually have nerve conduction defects that can manifest as motor impairment or sensory dysfunction. In quadrilateral space syndrome, compression of the axillary nerve and posterior humeral circumflex artery occurs. This compression produces poorly localized posterior shoulder pain, paresthesias over the lateral aspect of the shoulder and arm, and deltoid muscle weakness (Perlmutter, 1999). Acute nerve injury can cause temporary or persisting paralysis (Adams, 1992). For example, presentation of acute axillary nerve injury is quite variable. Presentation can include weakness in shoulder elevation with abduction and numbness, and paresthesias throughout the lateral arm can occur (Perlmutter, 1999). Nerve injury from anterior shoulder dislocations can cause paresis and an inability to move the arm (Visser, 1999). Studies have demonstrated that paresis of the deltoid muscle is the best indicator of nerve injury after one week (Visser, 1999).

The sensory component and motor component must be evaluated separately to ensure accurate diagnosis. In 1999, Visser et al reported that early-stage detection of nerve injury can be conducted through sensory testing of the axillary and musculocutaneous nerves. However, these results cannot provide a reliable indication of lesions of the motor nerves (Visser, 1999).

In some cases, the injury does not match the clinical presentation. Operative findings of nerve injury may or may not match clinical

findings. Data exist of gross operative evidence of nerve injury without clinical evidence of neurological dysfunction, such as with sheath hematoma and compression by fracture fragments. Conversely, data exist of intraoperative grossly normal-appearing nerves with clinical paresis (Cornwall, 2000). These deficits may develop after initially appearing with a normal neurological examination.

More specifically, following a traumatic hip dislocation, some patients may develop sciatic nerve deficits even after an initial normal neurological examination (Cornwall, 2000). Hence, when a nerve is damaged, it may continue to appear normal in a neurological examination. In truth, damage can be revealed only through diagnostic studies. Despite a normal neurological examination after a shoulder dislocation, Toolanen et al reported electromyographic evidence of axillary nerve injury in 8 of 65 patients in 1993 (Perlmutter, 1999).

In many instances, acute nerve injury associated with complex trauma complicates a thorough neurological examination. For example, of the patients with traumatic hip dislocations who are treated in the emergency department, many also present with concomitant head, visceral, or skeletal injuries. With these cases, a thorough neurological examination of the affected extremity becomes difficult to perform (Cornwall, 2000). Furthermore, in many patients, nerve injury may remain undetected because joint and/or bony injury may dominate the clinical picture (Perlmutter, 1999).

Certain presenting traumas should alert the clinician to the possibility of associated nerve injury. For example, for patients with trauma and obvious skeletal deformities to the shoulder, such as glenohumeral dislocation and/or fracture, be aware of the potential for associated nerve injury (Perlmutter, 1999). Nerve injury may be apparent immediately after injury. For example, immediate paralysis of common peroneal nerve function and foot drop with loss of eversion of the foot usually are reported at the time of a stretch/contusion injury without fracture or dislocation at the knee level (Kim, 1996). In an aggravated patient who is vigorously moving all of his extremities, a motionless upper extremity strongly suggests brachial plexus involvement (Cornwall, 2000).

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Surgical intervention for acute nerve injury is based on the extent of damage to the nerve and the nerve's functional viability. Consider each patient on an individual basis. When evaluating patients for surgery, surgeons should consider the location, the extent of the injury, the patient's age, and the patient's medical condition. Two important questions to consider before surgery are whether function can be obtained from the repaired nerve and whether the potential benefit to

the patient outweighs the surgical risks, costs, and loss of productivity (Schwartz, 1999). For example, adults older than 40 years rarely achieve a functional result from ulnar nerve repairs proximal to the elbow (Grant, 1999). Consequently, these patients may not be candidates for surgery.

Deciding the timing of surgery is very important. In clean lacerating injuries in which the nerve ends are visible in the wound or when clinical examination reveals obvious motor and sensory deficits resulting from the injury at the laceration, immediate primary repair may be indicated (Colohan, 1996). In blunt transections resulting from lacerations, delayed repair has a better surgical result (Kim, 1996). Injuries that do not demonstrate evidence of early spontaneous recovery, such as those caused by bullets, crushing blows, traction, fractures, or injections, are explored 2 months after the injury. For a nerve injury within 2-3 inches of recoverable muscle, 2 months is required for the growing axons to begin the process of muscle reinnervation. Therefore, an additional delay of 1 month is justified before surgical exploration. Brachial plexus stretches or contusions are observed for 4 months. If no evidence of recovery is present, the plexus is explored (Colohan, 1996).

Because nerves in the elbow are anatomically vulnerable, many researchers recommend early surgical exploration after fractures of the humerus (Ristic, 2000). Justification for late exploration is to allow sufficient time for spontaneous recovery. For example, for patients without functional recovery of the radial nerve, the time frame for late exploration ranges from 8 weeks to 5 months (Ristic, 2000). This allows sufficient time for spontaneous recovery without jeopardizing the results of late repair (Ristic, 2000). In 1999, Perlmutter mentioned that for injuries consistent with nerve rupture (eg, glenohumeral dislocation), a 3- to 6-month period without clinical or electrophysiological evidence of recovery warrants surgery. This time frame is sufficient for neurapraxic and axonotmetic injuries to resolve but is not long enough to jeopardize results of subsequent axillary nerve surgical repair (Perlmutter, 1999).

In the case of traumatic hip dislocation with a successful closed reduction, a short period of conservative treatment is recommended before surgical exploration (Cornwall, 2000). Different opinions exist with regard to how much time to allow for nerve function to return. More specifically, if nerve function does not return within 1 week, Nerubay et al (1973) advised surgical exploration. Stewart et al (1954, 1975) allowed 2 weeks, while Proctor (1973) allowed as many as 3 weeks for nerve function to return before performing exploratory surgery. On the other hand, Bromberg and Weiss (1977) recommended surgical exploration if nerve function has not returned within an 8- to 10-month period (Cornwall, 2000).

When certain cases are unresponsive to conservative treatment, surgery is the only alternative. For example, the pathogenesis of the quadrilateral space syndrome is poorly understood. Therefore, reserve surgery for patients in whom symptoms persist despite appropriate conservative treatment (Perlmutter, 1999). In cases of late sciatic nerve dysfunction from heterotopic ossification or scar tissue, a different controversy arises regarding surgical exploration. Several authors recommend surgical exploration as soon as the diagnosis becomes evident (Cornwall, 2000). However, Proctor (1973) cautioned against late sciatic nerve exploration because of the probable presence of scar tissue and/or heterotopic ossification and the consequent risk of iatrogenic nerve injury (Cornwall, 2000).

Surgery is indicated for patients with neurotmesis (Sunderland grade III-V) (Ristic, 2000). Therefore, accurate grading of an acute traumatic injury is essential. Accurate grading is necessary for identifying high-grade injuries that may benefit from early surgery and for preventing unnecessary early exploration of grade I and II lesions (Ristic, 2000).

Evolution of nerve injuries is important in indicating the need for open treatment (Ristic, 2000). If nerve function is progressively deteriorating as per electrodiagnostic study findings, surgery may be indicated because the status of the connective tissue cannot be assessed without direct exploration (Ristic, 2000).

RELEVANT ANATOMY AND CONTRAINDICATIONS

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Relevant Anatomy: Peripheral nerves are comprised of axons and associated Schwann cells enclosed in a basement membrane (Schwartz, 1999). Schwann cells ensheathe individual axons in myelinated fibers and groups of axons in unmyelinated fibers (Grant, 1999). The basement membrane is surrounded by thin collagen fibers called the endoneurium. The axon and Schwann cell composite are termed the endoneurial (Schwartz, 1999) or Schwann (Trumble, 2000) tube. Endoneurial tubes are grouped together, forming a variable number of fascicles.

Perineurium surrounds each fascicle. Perineurium is composed of collagen fibers and concentric layers of closely packed flattened cells, united by tight junctions. The perineurium creates a diffusion barrier against the surrounding environment, similar to the blood-brain barrier. The perineurium maintains a positive intrafascicular pressure and protects against infection.

Epineurium surrounds the layers of perineurium. The epineurium that

fills the space between fascicles is called internal epineurium, and epineurium surrounding the nerve is termed external, or outer, epineurium. The internal epineurium functions as a cushion for the fascicles. Where peripheral nerves span joints and where greater compressive forces are applied, the thickness of the internal epineurium is increased. The outer epineurial layers are composed of collagen and some elastin fibers (Schwartz, 1999).

Anatomic fascicular groups are formed by condensations of internal epineurium. Interconnections between fascicles form a fascicular plexus (Trumble, 2000). While these fascicular plexuses are abundant in the proximal portions of peripheral nerves, few are located in the more distal part of peripheral nerves (Trumble, 2000; Townsend, 1994). The location and position of fascicles inside the nerve depend on the destination of the fascicle branch in the periphery (Schwartz, 1999).

The blood supply to peripheral nerves usually is via the mesoneurium or suspending mesentery (Townsend, 1994). The vasa nervorum is a longitudinal system of vessels within the nerve that allows circulation to continue even after some freeing of surrounding tissue (Santos, 2000; Townsend, 1994).

Contraindications: In general, contraindications to surgery usually result when the risks of surgery outweigh the benefits. Surgery should not be performed when a poor outcome is expected. Some surgical repairs initially contraindicated may be performed later. If a swollen and discolored peroneal nerve is encountered during an acute knee repair, it should not be resected; rather, waiting several months is better (Kim, 1996).

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Lab Studies:

- The workup of every patient with acute nerve injury begins with a complete history and a physical examination. The site of injury can be accurately localized from a precise neurological examination (Greenfield, 1997). In traumatic hip dislocations, immediate assessment of nerve function is important because potentially reversible nerve injury from compression-induced ischemia can rapidly progress to permanent loss of function (Cornwall, 2000). Routine electrodiagnostic testing can be used to support a clinical suspicion of nerve injury or to evaluate the nerve function in patients in whom a reliable neurological examination is impossible (Cornwall, 2000).

- Differentiating between a peripheral nerve problem and an injury involving the spinal cord, brain, bone, or soft tissue is crucial. After establishing baseline physical

examination findings, the physician must answer the following questions (Grant, 1999):

- Do the symptoms and findings localize to a lesion in the central or peripheral nervous system?
- Are the symptoms and findings consistent with a focal or a diffuse type of peripheral nerve problem?
- Is the nerve injury complete or incomplete?
- What is the grade of the peripheral nerve injury?
- Does clinical evidence indicate recovery or further neurological deterioration?

- As part of the physical examination, the strength of individual muscles or of muscle groups is graded. Additionally, a sensory examination is performed, which includes testing for light touch, pinprick, 2-point discrimination, vibration, and proprioception (Grant, 1999). In anterior dislocation of the shoulder, the sensory distribution of the axillary and musculocutaneous nerves are tested to detect nerve injury in the early stages (Visser, 1999).
- Nerve injuries that result in decreased blood supply only result in delayed nerve conduction velocity. Significant external compression producing partial nerve ischemia is indicated by a 10% decrease in nerve conduction across a localized region (eg, the carpal tunnel). This is the most sensitive laboratory test to document a nerve compression syndrome (Trumble, 2000).

Imaging Studies:

- Imaging techniques, such as radiography, computed tomography (CT) scan, and, most recently, magnetic resonance imaging (MRI) are valuable diagnostic tools for evaluating a peripheral nerve lesion (Grant, 1999).
- Many peripheral nerve injuries can be associated with other soft tissue or bone injuries that can be detected through radiographic findings.
  - Radiographs of the injury site help identify fractures or foreign bodies (Greenfield, 1997). For example, cervical spine fractures frequently are associated with brachial plexus injuries.
  - In the presence of phrenic nerve paralysis, chest radiographs demonstrate unilateral elevation of the diaphragm.
  - Midhumeral fractures are associated with radial nerve injuries; midforearm fractures of the ulna or radius are associated with median or ulnar nerve injuries, respectively.
  - Hip and proximal femur fractures are associated with sciatic nerve injuries, and femur fractures that are more distal are associated with peroneal or tibial nerve

injuries (Grant, 1999).

- Two to 3 months after median nerve entrapment following an elbow trauma, lucency in the supracondylar region appears on x-ray films. This lucency helps diagnose median nerve entrapment radiographically (Ristic, 2000).

- To rule out bony and ligamentous injuries, all patients with axillary nerve injury should have radiographs taken of the shoulder and cervical spine (Perlmutter, 1999).

- For resolving the fine anatomic detail of soft tissue, MRI has proven to be much more effective than CT scan. Conventional MRI has been used to visualize both normal and abnormal peripheral nerve structures. In addition, MRI can help detect signal changes in denervated muscle as early as 4 days after injury. In a prospective study, MRI was sensitive and specific for evaluating ulnar nerve entrapment at the elbow, with 97% diagnosis of ulnar neuropathy (Britz, 1996). With the short tau inversion recovery (STIR), signals of the thenar muscles on MRI images were found in 100% of patients with clinically advanced carpal tunnel syndrome (Grant, 1999). With neuropraxic nerve injuries, STIR or T2-weighted signals in the innervated muscles remained normal. Therefore, following a peripheral nerve injury, obtaining an MRI of the muscle can be useful early in distinguishing a neuropraxic grade of injury from more severe axonotmetic and neurotmesis grades of injury.

- Because CT scan and traditional MRI techniques have inherent limitations in their capacity to resolve and distinguish peripheral nerves from the surrounding structures, magnetic resonance neurography (MRN) has been developed (Grant, 1999). An MRN can help visualize both normal and abnormal peripheral nerves in various regions of the body (Kuntz, 1996). The injured peripheral nerve can be assessed by orienting the images along the damaged nerve course. For example, the loss of T2-weighted signals indicates damage to the myelin sheath (Trumble, 2000). In addition, loss of water content in denervated nerves of deep muscles can be assessed by MRN when needle electrode tests are difficult to perform (Trumble, 2000). Regarding the assessment of peripheral nerve trauma, the predictive value of MRN as a diagnostic tool has not been established.

- At present, operative exploration with intraoperative electrophysiological monitoring remains the criterion standard to treat traumatic peripheral nerve lesions that are not improving (Grant, 1999).

Other Tests:

- Clinicians can use other tests to evaluate peripheral nerve injuries. For example, clinical threshold testing can be used to evaluate sensory function in peripheral nerves. These tests determine the level of stimulus necessary to elicit a response. Semmes-Weinstein monofilaments are fine filaments that exert a discrete amount of pressure on the fingertips. They are used to perform threshold testing. Vibratory sense can be assessed through clinical threshold testing using a range from low frequency (30 Hz) to high frequency (256 Hz) (Trumble, 2000).

- Injuries disrupting part or all of the nerve produce changes on electromyogram (EMG)

findings within 3 weeks of injury (Trumble, 2000). In nerve dysfunction from elbow trauma, Ristic et al (2000) recommend that nerve conduction studies (NCS) be delayed 3-4 weeks. After an anterior shoulder dislocation with paralysis or severe paresis, an EMG should be performed within 3 weeks (Visser, 1999). Severe nerve compression syndromes also can produce axonal disruption resulting in EMG changes (Trumble, 2000). In axillary nerve injury, results of EMG studies may show signs of deltoid muscle denervation, including fibrillation potentials (Perlmutter, 1999). Improved results from EMG studies without voluntary muscle contraction warrant further conservative therapy (Colohan, 1996). Repeat EMG studies are warranted if no clinical improvement occurs (Perlmutter, 1999).

- NCS are effective tests for evaluating peripheral nerve injury (West, 1994). Somatosensory evoked potential (SSEP) monitoring is accomplished through stimulation of a peripheral nerve. The SSEP is recorded from a scalp electrode over the contralateral sensory cortex. If signal conduction is disrupted along any segment of the circuit, an evoked potentiation will not be produced (Grant, 1999; Trumble, 2000).

- NCS are useful for distinguishing neurapraxic from more severe grades of injury. The hallmark of a neurapraxic injury is slowing or block of conduction across a section of nerve. The absence of nerve conduction distal to the injury indicates axonal loss related to a more severely graded injury (Grant, 1999).

- Nerve function and suspected injury can be tested with simple office techniques that do not require elaborate instruments.

    - Impending sciatic nerve dysfunction from traumatic hip dislocation can be predicted by a positive result on a sciatic stretch test. In this test, the examiner passively extends the affected knee with the hip flexed, which produces pain in the sciatic nerve distribution (Cornwall, 2000).

    - An advancing Tinel sign is another office technique that can be used to establish the progression of axonal regeneration (Grant, 1999).

Histologic Findings: Light microscopy of nerves injured by epineurectomy and nerve crush injury reveals widespread fiber degeneration and myelin debris in the subperineurial region (Santos, 2000). The centrofascicular areas have relative preservation compared to the subperineurial regions. The central vessels are preserved within the centrofascicular area of the injured nerve (Santos, 2000). In injured animals, the thickness of the myelinated axon area and myelin is less than in uninjured animals (Santos, 2000).

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Medical therapy: The goal of treatment is to return function to the damaged nerve and, at minimum, to improve the quality of life of patients. Not only is the nerve treated, but exogenous sources of nerve injury also are treated. Bone dislocation with neurological deficit requires prompt anatomical reduction to prevent irreversible nerve necrosis (Cornwall,

2000).

The use of analgesics can help patients control pain from nerve injuries (Perlmutter, 1999). Antivirals and steroids help to decrease endoneurial edema, an etiology of nerve injury (Santos, 2000). Hyperbaric oxygen (HBO) is an approved adjunctive treatment for acute traumatic ischemic reperfusion injury (Santos, 2000). HBO decreases endoneurial edema and pressure and vascular compromise of the vasa nervorum (Santos, 2000). Ciliary neurotrophic factor (CNTF) enhances motor neuron survival both in vivo and in vitro. Because CNTF continues to undergo research, whether or not patients will benefit from this treatment remains uncertain (Newman, 1996).

Surgical therapy: Primary repair is direct reconnection of the nerve immediately after injury. In an epineurial repair, the epineuriums of the separated nerve endings are sutured together using a microsuture (usually 8-0 or 10-0 Ethicon) (Townsend, 1994). Best results occur when the nerves are either purely sensory or purely motor and when the intraneural connective tissue component is small (this can vary from 22-80%) (Trumble, 2000; Townsend, 1994) and the fascicles have been clearly aligned.

Sharp lacerations without loss of nerve substance or partial lacerations with proper alignment are good examples of injuries that benefit from epineurial repair. In a crushing or delayed repair requiring trimming of the nerve ends, group fascicular repair improves fascicular alignment without an excessive number of sutures. Excessive sutures add to scar tissue production. Individual fascicle repair is not practiced widely because it requires numerous sutures and because it is technically difficult. (Trumble, 2000).

Secondary repairs are delayed repairs that may entail different strategies. Bones can be shortened to add length to a nerve. Nerve transposition across a flexed joint (eg, the ulnar nerve in the elbow) is another strategy for gauging nerve length in secondary repairs (Trumble, 2000). These techniques can gain as much as an approximate 10% increase in available nerve length (Trumble, 2000). However, within 3 weeks after injury, a nerve may lose as much as 8% of its length (Trumble, 2000). Many surgeons prefer delayed suture to primary suture because this allows the wound to heal and it decreases the risk of infection. In addition, during a delayed repair, scarred ends of the nerve can be defined more accurately and trimmed back to normal fasciculi. The epineurial suture is more secure because the sheath has toughened (Colohan, 1996). The suture of a severed nerve should not be delayed beyond 1 month (Colohan, 1996).

Neurolysis is performed on intraneural and extraneural scar tissue to release regenerating nerve fibers in the hope of improving functional recovery (Greenfield, 1997). Contaminated wounds, such as gunshot wounds and avulsions with severe tissue disruption, benefit from a secondary repair (Greenfield, 1997). Severely damaged nerves may require a nerve graft. For example, a graft would be necessary if, after resection of injured nerve ends (including neuroma), the defect could not be closed without tension (Townsend, 1994).

Studies show that sensation can return after nerve grafting (Bertelli, 1998). The sural nerve is the criterion standard for nerve autografts because of a favorable ratio of axons to epineuriums (Trumble, 2000). Loss of the sural nerve produces only a well-tolerated sensory loss on the lateral foot. Extensive research has focused on the use of allograft nerves to replace peripheral nerves that require a long nerve graft. Allografts can survive if the patient

is immunosuppressed and if the nerve allograft is preserved to maintain cell viability. Immunosuppression can be discontinued when the nerve graft has been incorporated with an ingrowth of Schwann cells from the host nerve ends. Nevertheless, results from autograft use are slightly more favorable than allograft use (Trumble, 2000).

Artificial conduits have not proven to be as successful as conventional nerve autografts (Trumble, 2000). Brain-derived neurotrophic factor (BDNF) and collagen tubulization have been used in an attempt to create a reliable artificial conduit for axonal regeneration (Utley, 1996).

Nerve or tendon transfers may be necessary for unrestorable or unsuccessful nerve repair. Brachial plexus injuries are not always reparable. In such cases, neurotizations or nerve transfers may offer a better functional outcome. The spinal accessory or long thoracic nerve can be grafted onto distal arm nerve trunks, with some improvement in elbow flexion (Colohan, 1996; Samardzic, 2000). When repair cannot or does not provide adequate results, planned tendon transfers can increase extremity function (Colohan, 1996). Tendon transfers, such as the posterior tibialis tendon passing through the interosseous membrane, can add power to a foot with a peroneal deficiency (Cornwall, 2000). Do not perform tendon transfers prior to 3 months after injury because early surgical exploration with nerve graft placement yields better results compared with primary tendon transfer (Ristic, 2000).

Preoperative details: Preoperative details include determining the type of surgery to be performed and the time frame. For example, open injuries may require immediate surgery and closed injuries may require reduction (in cases of dislocations or fractures) and monitoring (Grant, 1999).

Sunderland suggests 2 criteria that must be present before fascicular repair or interfascicular grafting is considered. The fascicular bundle must be large enough for suturing and must be sharply localized or sufficiently well defined so that it can be identified and mobilized for repair (Colohan, 1996). Preoperative testing with SSEP, CT scan, EMG, and MRI has improved diagnostic accuracy (Samardzic, 2000). The extent of surgical exploration is adapted to the reliability of the preoperative diagnosis (Samardzic, 2000).

Intraoperative details: Intraoperative electrodiagnostic monitoring is important for assessing the functional integrity of motor and sensory peripheral nerves. The patient is draped to allow observation of the tested muscle groups. Intraoperative SSEPs and direct electrical stimulation can be used. Regional and local anesthetic blocks or tourniquets are avoided to facilitate intraoperative electrophysiological testing (Grant, 1999). Surgically resecting scar tissue may prevent pain and promote healing (Grant, 1999). Keeping the nerve ends moist is important (Townsend, 1994). Ocular loupes are useful for lower magnification and wide-field dissections and are very helpful in preparing the ends of nerves and vessels for repair (Schwartz, 1999). The nerve can be protected during surgery by reducing tension through joint and limb manipulation and shielding with a blunt retractor to prevent iatrogenic injury (Perlmutter, 1999).

Surgical exploration with intraoperative nerve stimulation helps determine if neurolysis is the only intervention necessary (West, 1994). In a group of patients in whom treatment failed and who underwent operation for isolated and combined axillary nerve injuries, twice as many neurolyses as nerve grafts were performed compared to a group of patients who had

successful treatment. (Bonnard, 1999).

Postoperative details: Grant et al (1999) do not advocate the traditional several weeks of immobilization. Patients should undergo regular physical therapy to maintain a range of movement and to optimize the recovery of motor function as muscle reinnervation occurs (Grant, 1999; Greenfield, 1997). A short period to allow healing and adequate strength of the repair site is advised (Grant, 1999). Protect repairs by relaxed joint posturing for approximately 3 weeks (Schwartz, 1999). To prevent disruption of sutures at the repair site, the patient should avoid overzealous physical activity (Grant, 1999). In nerve transfers, the extremity is immobilized for 4 weeks after surgery, at which time physical therapy is initiated (Samardzic, 2000). Postoperative clinical and electrodiagnostic examinations are performed every 3 months for the first 2 years after surgery and every 6 months thereafter. (Samardzic, 2000).

Follow-up care: Clinical outcome is documented by serial clinical examinations and electrodiagnostic studies (Grant, 1999). Axillary injuries constitute an important clinical problem that requires close clinical and electrophysiologic evaluation during the months after the injury (Perlmutter, 1999). As a general rule, Grant et al (1999) suggested examining patients at 2 weeks, 6 weeks, 3 months, 6 months, 1 year, and then at yearly intervals if necessary and practical after surgery (Grant, 1999). Test and document range of movement and recovery of strength and sensation at each visit. Electrodiagnostic studies can help detect early signs of muscle reinnervation, several months before clinically evident muscle contractions appear (Grant, 1999). After nerve transfer surgery, assess patients 3 years after surgery (Samardzic, 2000). In most cases, maximal recovery requires as long as 24 months (Samardzic, 2000). An advancing Tinel sign suggests, but does not prove, regeneration of the nerve (Colohan, 1996; Kim, 1996).

COMPLICATIONS

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Following acute nerve injury, a variety of pain syndromes can develop (Colohan, 1996). Plexus or root avulsions may produce burning dysesthesias and paresthesias (Colohan, 1996). Painful neuromas and entrapment syndromes can arise at the site of injury and cause extreme local tenderness and pain (Colohan, 1996). Partial nerve injuries of mixed motor and sensory function can lead to causalgia. Symptoms include severe hyperesthesia, hypersensitivity to cold or muscle activity, and increased pain in stressful situations (Colohan, 1996). Paralysis can complicate nerve injury and sometimes cannot be repaired. If physical therapy is not instituted promptly after surgery, denervation can develop and result in muscle atrophy and fibrosis, joint stiffness, motor endplate atrophy, and trophic skin changes (Greenfield, 1997).

OUTCOME AND PROGNOSIS

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The outcome and prognosis of acute nerve injury varies widely among the different types of injuries and the type and timing of therapy. Patient compliance and motivation for recovery

also can have an important impact on the success of recovery (Schwartz, 1999). In traumatic hip dislocations and fracture dislocations, at least partial return of nerve function can be expected in approximately 60-70% of patients (Cornwall, 2000). The extent of injury to neural tissue, contamination of the wound, and the age and medical status of the injured patient are important factors influencing the outcome and prognosis of recovery (Colohan, 1996). Surgical delays in excess of 5 months dramatically decrease the rate of functional return (Bonnard, 1999). Therefore, schedule surgical repairs within 3 months following the injury (Bonnard, 1999).

Neuropraxic injuries usually are reversible, and patients recover within days to weeks (Grant, 1999; Greenfield, 1997). In axonotmesis, although axons will regenerate, functional recovery depends on the associated injuries, the amount of healthy proximal axon remaining after injury, and the age of the patient (Greenfield, 1997).

In addition, recovery usually is complete unless the injury is so proximal that atrophy of the motor endplate or sensory receptor occurs before the axon can grow back to these organs (Colohan, 1996; Trumble, 2000). A loss of cross-sectional area without any loss in muscle fiber count begins within 1 week of denervation (Schwartz, 1999). Recovery from axonotmetic injuries usually occurs over months (Grant, 1999). In neurotmesis, regeneration occurs but function rarely returns to normal (Greenfield, 1997). Intraoperative care with proper axial orientation of fascicles, proper coaptation, suture material, hemostasis, and suture line tension leads to better outcomes (Greenfield, 1997). Tension of the suture line and inadequate preparation of the nerve stumps are 2 leading causes of regenerative failure across the suture site, resulting in poor recovery of nerve function (Grant, 1999).

Spontaneous recovery (which occurs in two thirds of cases) may occur as late as 11 months after a gunshot wound. However, recovery after shotgun wounds is lower, with a 45% incidence rate of recovery (Colohan, 1996). Neural injuries associated with fractures have a greater than 80% incidence rate of spontaneous resolution. Recovery is less common with neural injuries secondary to dislocations (Colohan, 1996). Lesions resulting from shoulder dislocations recover within 12-45 weeks (Visser, 1999). Prior radiation therapy impairs cell division. This may affect Schwann cell division after nerve injury (Adams, 1992).

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In future research, decreasing the variability of injury and of functional recovery measurements hopefully will increase the sensitivity of the system to evaluate neuropathology and experimental interventions (Santos, 2000).

> Developing the ideal nerve injury model that can simulate acute hypoxic nerve injuries and be evaluated by functional models for regeneration is important to obtaining a greater understanding of neuropathophysiology and potential therapeutic interventions (Santos, 2000).

Experimental surgical techniques are being explored. In one repair technique, the injured nerves are frozen at the time of sectioning and repair and a protective solution is used to

bathe the cut ends of the nerve during repair. Synthetic tubules have been used to encase the sectioned end of an injured nerve to allow regrowth. This technique seems to offer comparable or better results than suturing the nerve ends (Colohan, 1996).

Metabolic manipulations using pulsating electric fields across a nerve repair and administration of a variety of biochemicals, including thyroid and adrenal hormones, anti-inflammatory agents, and other agents known to influence neurite growth in vitro, are being explored in experimental studies of nerve injury (Colohan, 1996). Clinical trials using trophic molecules to enhance axonal regeneration over time include insulinlike growth factors 1 and 2, NGF, BDNF, and neurotrophin 3 and 4/5 (Grant, 1999). Vascularized nerves can be useful to repair nerves longer than 8 cm and grafts placed in poor vascular beds that are heavily scarred (Townsend, 1994).

The use of MRI before surgery may be standardized in the future. Having a picture of the nerve anatomy before performing the surgery is valuable tool (Cornwall, 2000).

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Acute Nerve Injury excerpt

GENE EXPRESSION PROFILING IN THE NERVOUS SYSTEM FOLLOWING TRAUMATIC SPINAL CORD INJURY

Release Date: December 20, 2000

NOTICE: NS-01-004

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS)
REQUEST FOR INFORMATION (RFI)

The National Institute of Neurological Disorders and Stroke (NINDS), NIH is seeking to identify sources that are interested to develop capabilities for characterizing gene expression patterns in the mammalian spinal cord following traumatic injury.

Introduction and Background

The NINDS is the lead government agency for funding of research on spinal cord injury (SCI). Over 250,000 Americans are now paralyzed because of this condition and require specialized care and accommodation for everyday life. Since injury to the central nervous system (CNS) is a very complex phenomenon, research has often been limited to very specific molecules or mechanisms. New technology in the area of molecular biology greatly increases the ability to investigate many changes in gene expression that might occur under this circumstance. Under this solicitation, projects will develop capabilities for characterizing gene expression patterns in the mammalian spinal cord following traumatic injury. Research efforts will employ available neural tissue-specific and/or species-specific cDNA reagents and contemporary high throughput methodologies to quantify expression profiles of genes in acute and chronic phases of SCI. Changes in expression will be characterized at the injury site as well as in areas of the cord rostral and caudal to the lesion site. In addition, regions of brain that represent areas that project to or receive input from the spinal cord will also be evaluated for alterations in gene expression. The injury paradigm will utilize a well-characterized and justified rodent model of spinal cord trauma. Since the CNS is a complex structure, patterns of expression of specific genes will be characterized by in situ hybridization.

Precise spatial-temporal expression of genes during development is critical for determining and maintaining the structure and function of the mammalian nervous system. Numerous studies have identified factors that influence cell fate, expression of transmitters or growth factors, and guidance cues for axonal growth and dendritic arborization. These changes may be highly relevant to the adult system after trauma or during disease processes. It is not clear, however, to what extent such developmentally active molecules may be re-expressed after injury or during regeneration. Certainly, the expression of a multitude of genes and gene products associated with neuronal development--relating to neurite outgrowth, sprouting of fibers, cell survival--may be affected and changed at critical times after injury. For many years, researchers in the field of SCI have hypothesized that the failure of regeneration in the adult CNS is due primarily to the creation of a hostile "injury milieu"; might changes in expression patterns be correlated with an environment that prevents regeneration?

Analysis of changes in the multitude of proteins or mRNA patterns after injury is a daunting task. Up until now, investigators have studied particular proteins (i.e., GAP-43) or classes of proteins (i.e., cytoskeletal proteins, trophic factors) in the hope of finding evidence for involvement in regenerative responses. The development of new technologies to screen large numbers of genes or known sequences for expression after injury may focus the search for the critical elements in acute, sub-acute and chronic stages of

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injury. Obviously, a complex condition such as SCI has critical temporal and anatomic parameters. Prevention of outgrowth may occur at the injured axon tip or at the cell body. Negative or positive factors are likely expressed from the time of the injury through several stages of recovery and stabilization. Therefore, analysis should include comparative time frames after trauma, and various parts of the neuroaxis that may react differently to the injury, regeneration or stabilization phases.

Goals of the Contract

1. Chips and micro-arrays made with cDNA from rodent nervous system (rat and mouse), and from whole animal (mouse) are available, and can be used to create maps of gene expression after SCI. This contract will require the development and application of high-throughput approaches and technologies to quantify expression profiles of genes in rodent spinal cord following trauma. The investigators who undertake the project must understand and have available a relevant rodent model of adult SCI.

2. There will be systematic comparisons of expression patterns for different regions of the cord, as well as at different timepoints following injury. The technology will be applied to at least 6 time points representing acute (hours to days), subacute (days to weeks), and chronic (weeks to months) time windows to capture degenerative, regenerative, or stabilized patterns of reaction to injury. In addition, several different areas will be sampled with respect to the injury site, including areas immediately rostral and caudal to the lesion as well as other segments (i.e., if lesion is at thoracic level sample cervical and lumbar as well). In order to maximize the information gained from the studies, mRNA samples should be collected from relevant regions of the neuroaxis to sample cell bodies of projection neurons (i.e. cortex, brain stem, dorsal root ganglia), as well as local spinal cord circuits.

3. It is not the purpose of this contract to duplicate large scale production of specific chip or array technology at participating centers. Technology should be available for use or purchase.

4. Investigators will be required to provide data on gene expression, localization of gene products or other results of the contract to NIH databases for dissemination.

Feedback is sought from the research community on the following:

o The selection of time points after injury;
o Levels of sampling;
o Selection of genes;
o Methodologies (i.e. SAGE, micro-arrays, etc.)
o Databasing requirements; and
o Possible animal models of SCI and control tissues

This Request for Information (RFI) is for information and planning purposes only and shall not be construed as a solicitation or as an obligation on the part of the Government. The Government does not intend to award a contract on the basis of responses nor otherwise pay for the preparation of any information submitted or the Government's use of such information. Acknowledgment of receipt of responses will not be made, nor will respondents be notified of the Government's evaluation of the information received. However, should such a requirement materialize, no basis for claims against the Government shall arise as a result of a response to this request for information or the Government's use of such information as either part of our evaluation process or in developing specifications for any subsequent requirement.

Neuromuscular Disorders

Conditions that affect components of a motor unit (motor neuron cells of the spinal cord, nerve, neuromuscular junction, and muscle fibers), sensory and autonomic nerves or their supportive structures are included in the broad category of neuromuscular disorders. Listed below are brief discussions of commonly recognized neuromuscular conditions and are intended for general public, students, residents, and nonspecialists. Disorders of motor neurons are covered on the web page for Amyotrophic Lateral Sclerosis Research and the MDA/ALS Clinic.

Myopathies:

- Polymyositis
- Dermatomyositis
- Inclusion Body Myositis
- Muscular Dystrophies
- Metabolic Myopathies

Disorders of Neuromuscular Junction:

- Myasthenia Gravis
- Eaton-Lambert Syndrome

Neuropathies:

- Guillian Barre Syndrome
- CIDP
- Diabetic Neuropathy
- Hereditary Neuropathies

Department of Neurology, Baylor College of Medicine

Comments to: neurons

URL:http://www.bcm.tmc.edu/neurol/index.html

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Responses will be held in a confidential manner. Any proprietary information should be so marked.
All respondents are asked to indicate the type and size of your business organization, e.g., Large Business, Small Business, Hubzone Small Business, Small Disadvantaged Business, Women-Owned Business, 8(a), Historically Black College or University/Minority Institution (HBCU/MI), educational institution, profit/non-profit hospital, or other nonprofit organization.

Responses should be identified with NINDS RFI No. 01-004, and are due by January 5, 2001. Please submit three (3) copies of your response, not to exceed 5 pages, to the attention of: Laurie A. Leonard, Contracting Officer, Contracts Management Branch, National Institute of Neurological Disorders and Stroke, NIH, 6001 Executive Boulevard, Room 3287, MSC 9531, Bethesda, Maryland 20892-9531. Facsimile (301-402-4225) responses will also be accepted as long as they do not exceed 5 pages in length. E-mail responses, sent to LL44S@nih.gov, will also be accepted.

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Department of Health and Human Services

National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892

Neuromuscular Diseases

Muscle Diseases (Myopathy)

Dermatomyositis (DM): DM is an *auto immune* muscle disease which occurs in children and adults. The cardinal sign of this disorder is the presence of a rash commonly over the upper chest and back or shoulders. Occasionally, a purplish (heliotrope) discoloration is present over the eyelids. Along with the rash, muscle weakness in the hips and shoulders is noted. The disease develops over weeks to months. The cause is unknown but involves inflammation of the blood vessels in the skin and muscle. Diagnosis is clinical with supportive evidence from blood levels of muscle enzymes (*CK or creatine kinase*), and EMG findings. Many people undergo muscle biopsy for a definitive diagnosis. The disease responds well to oral *steroids* but is sometimes resistant and may require treatment with azathioprine or *IVIG*.

Polymyositis (PM): PM is similar to *DM* but doesn't have the rash. Symptoms develop over weeks to months in most cases. The cause is usually unknown but occasionally, PM and DM are associated with cancer or rheumatoid conditions. Treatment is similar to that of DM.

Drug-induced myositis: Several medications may lead to muscle damage. These include certain cholesterol lowering agents, colchicine, and ipecac.

Inclusion Body Myositis (IBM): IBM develops more slowly than either *PM* or *DM*. Typically, a diagnosis is not reached for several years. Weakness is more asymmetric and there is no rash. The cause is unknown but may represent a degenerative condition with secondary inflammation as opposed to PM where inflammation is primary. Perhaps because of this, IBM responds less well to *steroids* and other immune suppressing therapies.

Muscular Dystrophy

Duchenne's muscular dystrophy (DMD): DMD is a progressive hereditary disease that presents in boys during infancy or early childhood. Affected children will be slow to walk and may fail to master certain motor activities by the appropriate age. Initially, patients have weakness in shoulder and hip girdle muscles initially but, over years, become weak in hand and foot muscles as well as respiratory and cardiac muscles. The disease progresses to death often by the age of 20 due to heart failure or respiratory compromise. A severe deficiency or absence of the protein dystrophin underlies this disease but the exact mechanism is unknown. Diagnosis is clinical with supportive evidence from *EMG* and *CK* elevation. Definite diagnosis is now possible by

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muscle biopsy or by genetic testing of blood. The disease partially responds to high doses of oral *steroids* but there is no cure. A milder form of DMD is known as Becker dystrophy and results from a partial loss of dystrophin. In some cases, women who carry the abnormal gene have some mild symptoms of muscle disease (cramps, slight weakness, mildly elevated CK) and are known as manifesting carriers.

Limb-girdle dystrophy(LGD): LGD may be a severe muscle disease beginning in infancy or becoming noticeable only during adulthood depending on the variety. In some cases there is an abnormality of a muscle membrane protein related to dystrophin (see *DMD*). Weakness is predominately located in the shoulder and hip girdle muscles. In affected adults the disease progresses slowly and is usually not life-threatening. This disease is inherited in some cases and there is no known treatment.

Myotonic dystrophy (DM): Unlike most muscular dystrophies, DM usually shows severe distal weakness prior to the development of proximal weakness. It is inherited in a dominant fashion (meaning an affected person has a 50% chance of passing the disease to each of his or her children). Symptoms can be evident at birth or not be noticeable until adulthood. Drooping of the eyelids (ptosis), swallowing muscles and cataracts are other frequent features of the disease. No cure or effective treatment is available.

Diseases of the Neuromuscular Junction

Myasthenia gravis (MG): *Auto immune* disease where the target of inflammation are the *acetylcholine receptors* on the muscle membrane. MG may occur at any age and common early symptoms are double vision, droopy eyelids, difficulty swallowing, or generalized weakness. The onset may be gradual over months or develop rapidly over several days or weeks. Diagnosis is clinical with supportive evidence including presence of acetylcholine receptor antibodies, positive tensilon test, or abnormal electrodiagnostic testing. A number or therapeutic agents are available and include *steroids*, *IVIG*, *plasmapheresis*, azathioprine, pyridostigmine and surgical removal of the thymus gland.

Acquired Nerve Diseases (Polyneuropathies)

Axonal Polyneuropathies

Diabetic polyneuropathy occurs in many patients with either insulin-dependent or non-insulin dependent diabetes mellitus. It's severity can be correlated to some degree with the severity and duration of hyperglycemia. The disease has a predilection for small *unmyelinated* nerve fibers which carry information on temperature and pain so that the early symptoms are reduced pain awareness and the inability to detect temperature. Paradoxically, the symptoms tend to be associated with burning of the toes or bottom of the foot. The symptoms develop symmetrically and often spare the hands. Significant weakness is unusual although it can be quite painful. Diagnosis is clinical and may be confirmed with *NCS*. Other causes may need to be ruled out. There are many medicines that ameliorate the pain (amitriptyline, nortriptyline, gabapentin, carbamazepine, capsaicin) but these do not treat the underlying neuropathy. A human

protein called Nerve Growth Factor (NGF) may help treat the underlying neuropathy and reduce the symptoms. NGF is being studied in a clinical research trial at BGSM and other centers around the country. *Click here* for information on this study.

Vitamin B12 deficiency may lead to a number of serious conditions including peripheral neuropathy. This may occur in persons who are strict vegetarians, people who are malnourished, and may also happen to otherwise healthy people on normal diets who develop pernicious anemia. In this *auto immune* disease, the body makes antibodies against its own cells in the gut lining which leads to an underproduction of intrinsic factor, the protein which is responsible for binding B 12 in the intestine and getting the vitamin into the bloodstream. Absence of the vitamin leads to anemia which is resistant to iron therapy and may cause neuropathy and a more serious condition of degeneration in the spinal cord called subacute combined degeneration. This may occur in addition to neuropathy and causes weakness, sensory loss and incoordination. The peripheral neuropathy of vitamin B12 is not unusual and presents with tingling/numbness in the feet sometimes associated with more painful altered sensations (dysesthesias). Weakness is uncommon except in cases where there is concomitant subacute combined degeneration. The diagnosis is confirmed by NCS and by testing the blood vitamin B12 level. One important point that is overlooked is that many patients with neuropathy from B12 deficiency do not have the anemia or changes in the white blood cells that frequently seen in this disorder. Treatment is with vitamin B12 injections or oral therapy depending on the severity of the deficiency and the underlying cause. Treatment may not be successful in completely restoring the nerves to pre-deficiency function.

Neuropathies associated with paraproteins: Paraproteins are abnormal proteins in the blood which are sometimes markers for malignancy but maybe of benign origin. Sometimes these are associated with nerve disease and cause a wide range of symptoms from severe sensory involvement to primarily weakness. These neuropathies are much more common in the older age groups (>60 yrs) and are often of mild severity. The neuropathy is slowly progressive but occasionally progresses more rapidly. The symptoms can be treated with medicines that ameliorate the pain (amitriptyline, nortriptyline, gabapentin, carbamazepine, capsaicin) but this doesn't affect the underlying neuropathy. When the disease is severe, treatment of the nerve disease can be attempted with *steroids* and other immunosuppressants.

Neuropathies associated with thyroid disease: There is an association between hypothyroidism and polyneuropathy. When it does occur the symptoms are typical of all neuropathies: tingling/burning and sharp, sudden, lancinating pain in the feet and hands. More commonly, *carpal tunnel syndrome* is a presentation of hypothyroidism.

Toxic neuropathies: Many drugs are known to cause neuropathy. The most common are the chemotherapeutic agents vincristine, cisplatinum, taxol. Some others include cyclosporine, metronidazole, dapsone, and amiodarone. Pesticide exposure can cause neuropathy. Rarely, heavy metal intoxication (lead, arsenic, mercury) can cause neuropathy.

Alcoholic neuropathy: Heavy alcohol use may cause a neuropathy which is mostly sensory. Burning and tingling in the feet is first noted and the involved area may ascend

differentiate them without nerve conduction studies (*NCS*) or genetic testing. The inheritance is dominant meaning a person with CMT has a 50% chance of passing it down to each of his or her children. Typically, CMT patients have unusually high arches noted from early in life but are normal into the teenage years. CMT children frequently turn their ankle and may be "clumsy" as they trip over their toes frequently. Sometimes the disease isn't recognized until patients are much older (40-60 yrs). Commonly, CMT patients complain of weakness more than numbness/tingling/burning despite profound involvement of their sensory nerves. The disease is slowly progressive and, although many patients need to wear a brace to help keep their feet from dragging, most patients are not disabled or wheelchair bound and have a normal life expectancy. Research has shown that the most common form of CMT (Type 1A) is caused by an overexpression of a *myelin* gene, PMP-22. The exact function of this protein is currently unclear and there is no current treatment for the underlying disease.

Hereditary Neuropathy with Liability to Pressure Palsies (HNPP): This disease is probably widely under diagnosed. Like *CMT Type 1A*, it is a *demyelinating* neuropathy and may be the result of an under dosage of a *myelin* protein (PMP-22) which is overproduced in CMT 1A. This disease should be considered in patients with multiple *entrapment neuropathies* as these are common in HNPP. Symmetrical burning/numbness/tingling in the feet may also be present. As in CMT, the exact cause is unknown and there is no treatment other than pain medicines and avoidance of entrapment neuropathies.

Entrapment (Compression) Neuropathies

Carpal Tunnel Syndrome (CTS): CTS is the most common entrapment neuropathy. Persons with CTS complain of tingling or numbness in their fingers especially the thumb, index and middle fingers. Occasionally, the tingling is irritating and awakens people from sleep or bothers them when they read the newspaper. Weakness is unusual but people often complain of dropping things if they aren't looking at them. CTS is caused by irritation of the median nerve as it passes from the middle of the wrist into the palm through a tunnel created by ligaments and bones called the carpal tunnel. CTS can be easily diagnosed by NCS and is treated with splinting the wrist at night in mild cases or surgical release of the ligaments which form the roof of the tunnel in more severe cases.

Ulnar Neuropathy at the Elbow: Another common entrapment neuropathy, this disorders typically begins with elbow pain with tingling ("hit your funny bone" sensation) in the ring finger and little finger. If the condition is left untreated, grip strength becomes reduced and the muscles of the hand may *atrophy* causing the tendons and bones to appear more prominent. Here, the ulnar nerve is irritated as it passes between two bones along the inside of the elbow (ulnar groove). This is also diagnosed with *NCS/EMG* and can be treated with splinting and padding the elbow, or with surgery. The surgery is more involved than in *CTS* as the nerve is typically moved out from the bones and is placed in the forearm.

Tarsal Tunnel Syndrome: This neuropathy is less common than the others and is more difficult to treat and diagnose. Tingling or pain along the toes and bottom of one foot is the most common presentation. Weakness of foot muscles is rare and it is

unusual for the symptoms to be in both feet. Ankle injuries may predispose people to have such symptoms. The tibial nerve is irritated as it passes between the Achilles tendon and the prominent bone at the inside of the ankle. *NCS* is occasionally useful in making the diagnosis but specialized testing may be necessary. In severe cases, surgeons can decompress the tibial nerve at the ankle by cutting the overlying ligaments. Surgery is less successful than in *CTS*.

Peroneal neuropathy at the knee: This usually occurs in people who cross their legs or squat for prolonged periods of time like gardeners. All of these maneuvers compress or stretch the peroneal nerve as it crosses over a bone (fibula) along the outside of the knee. Trauma is another common reason to develop this problem. People may become unable to flex their ankle upward (*foot drop*). Occasionally, there is also numbness along the outer portion of the calf or top of the foot. The weakness usually goes away by itself if the leg-crossing and squatting is discontinued. Surgery is rarely necessary.

Sciatic neuropathy: The sciatic nerve forms from after nerve roots from the lower lumbar and sacral spine participate in the plexus. The nerve has 2 divisions (peroneal and tibial) which divide behind the knee. Sciatic neuropathy would be an uncommon cause of "*sciatica*" and is most often seen in the setting of hip fractures or hip surgeries. Severe motor vehicle accidents and penetrating trauma also cause sciatic neuropathies. On occasion, these occur following improper placement of an intramuscular injection into the buttock. The so-called "wallet-neuropathy" produces mild sciatic symptoms after prolonged sitting on a hard surface. In this setting, generally male patients may complain of tingling/numbness on their feet or calves and with a mild *foot drop*. Wallet neuropathy resolves spontaneously after switching the wallet to the other pocket.

Nerve Plexus Diseases

Brachial plexopathy: The brachial plexus is a complicated network of nerves in the shoulder. These are commonly damaged in several settings including birth trauma, severe motor vehicle accidents and penetrating trauma (bullet and stab wounds), and due to lung and breast malignancies. Sometimes these occur without clear reason (*idiopathic*) and are called idiopathic brachial plexopathy. There are a variety of names for this disorder including neuralgic amyotrophy, Parsonage-Turner syndrome or brachial plexitis. The cause is unknown but may be *auto immune* or post-viral as this disorder often follows surgery or viral infections. Severe shoulder pain heralds the disease and may last for days to weeks. Following this, people may notice weakness, numbness, or *atrophy* of their muscles. Usually, there is spontaneous improvement without specific treatment. Some experts recommend a short course of oral steroids if the process is caught early while there is still pain.

Lumbosacral plexopathy: The lumbosacral plexus is a complicated network of intertwining nerves located in the pelvis. These nerves may be damaged following severe trauma or occur in relation to hip/pelvic surgeries. Occasionally, a hematoma from a catheterization procedure causes a plexopathy. *Idiopathic* lumbosacral plexopathies are much less common than idiopathic brachial plexopathies but may occur. One special type of lumbosacral plexopathy should be mentioned is *diabetic amyotrophy*.

Diabetic amyotrophy: This disorder is often seen in recently diagnosed diabetics and may be the first sign of the disease. Typically, there is the development over hours to days of severe pain in the groin and upper thigh followed by weakness of bending the hip and/or straightening the knee. The muscles of the upper leg may become *atrophied.* The disease may progress for some weeks then commonly improves spontaneously over months. Occasionally, amyotrophy occurs bilaterally. The cause is unknown but may be vascular in nature. To date there has been no treatment for this disease, although there are reports of *IVIG* and oral *steroids* being effective.

Nerve Root Diseases (Radiculopathy)

Cervical radiculopathy: Impingement of bone or disk material on a cervical nerve root can cause neck pain which radiates into the arm, weakness of arm and shoulder muscles, and numbness. The most common cervical radiculopathy is C6-7 which may cause neck/arm pain, weakness of the triceps, and numbness in the middle fingers. The C5-6 root tends to cause numbness in the thumb and index finger in association with deltoid and biceps weakness. The C7-8 root may cause numbness in the ring and little fingers in association with decreased grip strength or fine coordination of the fingers. If the symptoms are mild, no diagnostic testing may be necessary. If severe, an MRI scan of the neck and/or an *EMG* are helpful in confirming the diagnosis. Conservative therapy consists of warm compresses, cervical collar, physical therapy and occasionally traction. Surgery may be performed to decompress the nerve root by a neurosurgeon or orthopedic surgeon.

Lumbosacral radiculopathy: This is sometimes known as *sciatica*. Impingement of bone or disk material on a nerve root in the low back can cause pain which radiates into the hip, buttock, and leg. Numbness and weakness may also occur. The most common roots to be affected are the L4-5 and L5-S1 roots. L4-5 radiculopathies present with back pain, numbness on the outside of the calf and sometimes weakness of flexing the ankle upwards or *foot drop*. S1 root disease often causes numbness on the back of the calf and bottom of the foot associated with weakness on pointing the toe. If the symptoms are mild, no diagnostic testing may be necessary. Most low back pain resolves spontaneously within 2 weeks and current recommendations are to continue with your normal activities as much as can be tolerated. Prolonged bed rest should be avoided. Low back pain associated with weakness is more serious and an MRI scan of the lower back and/or and *EMG* are helpful in confirming the diagnosis. Conservative therapy consists of non-steroidal medications (such as ibuprofen), heating pads and physical therapy. A neurosurgeon or orthopedic surgeon can decompress the nerve root in the operating room.

Degenerative Disk Disease: As people age, the intervertebral disks become less pliable and more calcified like bone. Years of stress on the vertebrae cause constant breakdown followed by build up of new bone at the point where the vertebrae touch each other. The condition can mimic *cervical* or *lumbosacral radiculopathies*. Bony overgrowth may narrow the openings for the nerve roots (foramina) and will diminish the size of the spinal canal. This condition is called cervical stenosis in the neck and lumbosacral stenosis in the low back. The process can be accelerated through trauma, arthritis, obesity, and years of physical labor.

Cervical stenosis often presents with neck pain with or without radiation into the arms and with difficulty walking due to poor balance or leg stiffness/weakness. The diagnosis is clinical with supporting evidence from a cervical MRI scan or myelogram. If symptoms are mild, it can be treated with non-steroidal medications or sometimes with epidural injection of *steroids*. More severe symptoms can be treated with decompressive surgery.

Lumbosacral stenosis often presents with low back pain sometimes with radiation into the buttock or leg(s) but weakness is uncommon. Some patients with this disorder will have cramps (neurogenic claudication) in their calves or thighs. Sometimes symptoms can be relieved by bending over and flexing the spine forward. Back pain due to stenosis may also improve on walking as opposed to back pain from *lumbosacral radiculopathy* which may worsen with movement. The diagnosis is clinical with supporting evidence from an MRI scan or myelogram. If symptoms are mild, it can be treated with non-steroidal medication or sometimes with epidural injection of *steroids*. More severe symptoms can be treated with decompressive surgery.

Motor Neuron Disease

Motor Neuron Diseases are a group of diseases which are unified by their selective involvement of *upper and/or lower motor neurons*. There are likely to be multiple causes for these diseases even within the groupings listed below. Some points in common are that MNDs tend to relatively spare eye movements and bladder/bowel function.

Amyotrophic Lateral sclerosis (ALS) or Lou Gehrig's Disease: This disease affects both upper (UMN) and lower (LMN) motor neurons (see *principles of neuroanatomy*) producing progressive *spasticity*, weakness, and *atrophy* of the limb muscles. Typically, the disease begins with painless weakness and wasting of the muscles of one hand or one foot. Sensory complaints should not be present but muscle twitching or fasiculations may be noted. Another common presentation of this disease is the gradual onset of difficulty speaking (dysarthria) or swallowing (dysphagia). This is due to involvement of the *bulbar* muscles. The disease is progressive at a variable rate but is often marked by plateaus and extremely rare reports of spontaneous regression. Depending on the age of onset and the type of presentation, the average life expectancy is around 3 years. Some people live much longer with approximately 10% surviving longer than 10 years. The cause of this disease is unknown. Diagnosis is clinical with supportive evidence from NCS/EMG. Frequently, MRI scans of the brain or spine are necessary to rule out tumors or degenerative spine disease. Riluzole is the first drug to receive FDA approval for the treatment of ALS. The drug has been shown to extend the life expectancy of patients by several months.

There are several clinical syndromes that may be related to ALS but can also be caused by other disorders. They are named according to the type of motor neurons which degenerate. Progressive Muscular Atrophy (PMA) involves only LMNs, Pseudobulbar Palsy affects the UMNs of the face and throat muscles, Progressive Bulbar Palsy involves LMNs of the face and throat muscles.

BGSM is actively involved with ALS and, frequently, the physicians at BGSM are involved with clinical trials of experimental agents. *Click here* for an update on current research protocols offered at BGSM. Basic scientists at BGSM are also actively involved with the study of motor neuron development and survival.

Multifocal motor neuropathy with conduction block: This recently described disease may mimic *ALS*. Usually, there is a very slow development of weakness and wasting in one hand or arm with minimal sensory changes. UMNs do not degenerate in this disease. *NCS* may show conduction block, an electrophysiologic finding that suggests focal *axon* dysfunction or *demyelination*. This disease can respond dramatically to *IVIG*.

Polio: Unlike all the other motor neuron diseases considered here, polio has an abrupt onset, is self limited and improves spontaneously. Polio is caused by infection with the polio virus which begins with fever and lethargy and progresses to paralysis of all or some of the muscles. The majority of cases occur in infants and can occur following administration of the oral polio vaccine (OPV). The risk of contracting polio from the vaccine is 1 in 2.5 million. Recovery may be full or partial depending on the degree of *LMN* degeneration. Adults who suffered polio as a child frequently have scoliosis of the spine and atrophy of one or more limbs. These patients may develop a variety of symptoms (weakness, fatigue, pain) years after their infection known as the post-polio syndrome.

Spinal Muscular Atrophy (SMA): There are a variety of SMA disorders which affect infants and adults. These disorders affect only *LMN*s and in adults are very slowly progressive. One of the SMAs that can mimic ALS is Kennedy's disease or X-linked Spinobulbar Muscular Atrophy. As the disorder is linked to a gene on the X-chromosome and is *recessive*, only males will get the disease and females are carriers. Kennedy's Disease is marked by proximal weakness in the limbs and by weakness of facial muscles. Other features include a sensory neuropathy, decreased fertility, and enlarged breasts. This disease does not shorten life expectancy but may result in mild to moderate disability. [go to *featured topics*].

Monomelic amyotrophy: This rare form of MND usually affects <u>one</u> arm with weakness and wasting and occurs mostly in males in their teenage or early adult years. The disease may progress rapidly for 1-2 years then very slowly progress or halt with minimal recovery. This should not be confused with *ALS*. [ref Donofrio's article]

FILE

Applicant Thomas M. Jessell, et al.

Client Columbia (0575) File No. 57477-A-PCT-US Atty. JPW/MVM

Date May 11, 2004

Kindly acknowledge receipt of the accompanying

AMENDMENT IN RESPONSE TO FEBRUARY 11, 2004 OFFICE ACTION AND INFORMATION DISCLOSURE STATEMENT in connection with Thomas M. Jessell et al., for GENE ENCODING MNR2 AND USES THEREOF, U.S. Serial No. 09/820,598, filed March 29, 2001, including Transmittal Letter in Triplicate, PTO Form 1449 **(Exhibit A)**, PCT Search Report **(Exhibit B)**, articles **(Exhibits C-F)**, references **(Exhibits 1-58)**, a check in the amount of $180.00, and a Certificate of Mailing dated May 11, 2004.

Date Due: May 11, 2004.

by placing your receiving date stamp hereon and returning to us.

MPL

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MAY 19 2004

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by placing your receiving date stamp hereon and returning to us.

Applicants: Thomas Jessell et al.
U.S. Serial No.: 109/820,598
Filed: March 29, 2001
Exhibit IV

5714 1-A-PCUS JPW

UNITED STATES PATENT AND TRADEMARK OFFICE

MAY 2 8 2004

COMMISSIONER FOR PATENTS
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ALEXANDRIA, VA 22313-1450
www.uspto.gov

09/820598

DOCKET

Paper No.

Notice of Non-Compliant Amendment (37 CFR 1.121)

The amendment document filed on 5/13/04 is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003). In order for the amendment document to be compliant, correction of the following item(s) is required. **Only the corrected section of the non-compliant amendment document must be resubmitted (in its entirety), e.g., the entire "Amendments to the claims" section of applicant's amendment document must be re-submitted.** 37 CFR 1.121(h).

THE FOLLOWING CHECKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

☐ 1. Amendments to the specification:
- ☐ A. Amended paragraph(s) do not include markings.
- ☐ B. New paragraph(s) should not be underlined.
- ☐ C. Other _____

☐ 2. Abstract:
- ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
- ☐ B. Other _____

☐ 3. Amendments to the drawings: _____

☐ 4. Amendments to the claims:
- ☒ A. A complete listing of all of the claims is not present.
- ☐ B. The listing of claims does not include the text of all claims (including withdrawn claims)
- ☐ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified.
- ☐ D. The claims of this amendment paper have not been presented in ascending numerical order.
- ☐ E. Other: _____

5/25/04: 1 Mo: 6/25/04
2 Mo: 7/25/04
3 Mo: 8/25/04
4 Mo: 9/25/04
5 Mo: 10/25/04
6 Mo: 11/25/04
SML

For further explanation of the amendment format required by 37 CFR 1.121, see MPEP Sec. 714 and the USPTO website at http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/officeflyer.pdf.

If the non-compliant amendment is a **PRELIMINARY AMENDMENT,** applicant is given ONE MONTH from the mail date of this letter to supply the corrected section which complies with 37 CFR 1.121. Failure to comply with 37 CFR 1.121 will result in non-entry of the preliminary amendment and examination on the merits will commence without consideration of the proposed changes in the preliminary amendment(s). This notice is not an action under 35 U.S.C. 132, and **this ONE MONTH time limit is not extendable.**

If the non-compliant amendment is a reply to a **NON-FINAL OFFICE ACTION (including a submission for an RCE),** and since the amendment appears to be a *bona fide* attempt to be a reply (37 CFR 1.135(c)), applicant is given a TIME PERIOD of ONE MONTH from the mailing of this notice within which to re-submit the corrected section which complies with 37 CFR 1.121 in order to avoid abandonment. **EXTENSIONS OF THIS TIME PERIOD ARE AVAILABLE UNDER 37 CFR 1.136(a).**

If the amendment is a reply to a **FINAL REJECTION,** this form may be an attachment to an Advisory Action. **The period for response to a final rejection continues to run from the date set in the final rejection,** and is not affected by the non-compliant status of the amendment.

Vanessa Blythe (571) 272-0504
Legal Instruments Examiner (LIE) Telephone No.

Rev. 10/03

Applicants: Thomas Jessell et al.
U.S. Serial No.: 109/820,598
Filed: March 29, 2001
Exhibit V

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/820,598	03/29/2001	Thomas M. Jessell	57477-A-PCT-US/JPW/MVM	5690

7590 05/25/2004

Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
CARLSON, KAREN C	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 05/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Dkt. 57477-A-PCT-US/JPW/MVM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Thomas M. Jessell et al.

Serial No.: 09/820,598 Group Art Unit: 1653

Filed: March 29, 2001 Examiner: K. Carlson, Ph.D.

For: GENE ENCODING MNR2 AND USES THEREOF

1185 Avenue of the Americas
New York, New York 10036
June 25, 2004

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

COMMUNICATION IN RESPONSE TO MAY 25, 2004 NOTICE OF NON-COMPLIANT AMENDMENT (37 C.F.R. §1.121)

This Communication is submitted in response to a May 25, 2004 Notice of Non-Compliant Amendment (37 C.F.R. §1.121) issued by the United States Patent and Trademark Office in connection with the above-identified application. A copy of the Notice is attached hereto as **Exhibit A**. The Notice provides a one-month period for filing a response. Therefore, a response to the May 25, 2004 Notice is due June 25, 2004. Accordingly, this Communication is being timely filed.

REMARKS

The Examiner objected to applicants' May 11, 2004 reply to the February 11, 2004 Office Action for allegedly not having been submitted in the format required under 37 C.F.R. §1.121. Applicants note the date of May 13, 2004 erroneously attributed to the May 11, 2004 Amendment. Specifically, the

Examiner stated that the amendment does not include a complete listing of all of the claims.

Further to a June 16, 2004 telephone conference between Maria Marucci, Esq. of the undersigned attorney's firm and the Legal Instruments Examiner, Ms. Marissa Blyther, Examiner Blyther realized that the May 11, 2004 Amendment does indeed include a listing of all of the claims and, therefore, satisfies the requirements of 37 C.F.R. §1.121. Ms. Blyther stated that since the May 25, 2004 Notice was sent in error a response thereto is not required. Ms. Blyther stated that no communication would be sent by the Patent Office confirming that a response to the May 25, 2004 Notice is not required.

Therefore, applicants submit this Communication in order to make of record the June 16, 2004 telephone conference between Ms. Marucci and Ms. Blyther, wherein Ms. Blyther stated that a response to the May 25, 2004 Notice is not required.

In view of the above remarks, applicants maintain that the May 11, 2004 Amendment, together with the remarks and submissions made herein, satisfy the requirements of 37 C.F.R. §1.121.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

6/25/04

John P. White
Reg. No. 28,678

Date

57477-A-PCT-US JPW

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09/820598

Paper No.

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THE FOLLOWING CHECKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

5/25/04: 1 Mo: 6/25/04
2 Mo: 7/25/04
3 Mo: 8/25/04
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Hanson Blythe (571) 272-0504

Legal Instruments Examiner (LIE) Telephone No.

Rev. 10/03

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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7590 05/25/2004

Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
CARLSON, KAREN C	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 05/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE

Applicant Thomas M. Jessell, et al.

Client Columbia (0575) File No. 57477-A-PCT-US Atty. JPW/MVM

Date June 25, 2004

Kindly acknowledge receipt of the accompanying

COMMUNICATION IN RESPONSE TO MAY 25, 2004 NOTICE OF NON-COMPLIANT AMENDMENT (37 CFR §1.121) in connection with Thomas M. Jessell et al., for GENE ENCODING MNR2 AND USES THEREOF, U.S. Serial No. 09/820,598, filed March 29, 2001, including **Exhibit A** (copy of Notice) and a Certificate of Mailing dated June 25, 2004.

Date Due: June 25, 2004

by placing your receiving date stamp hereon and returning to us.

Applicant Thomas M. Jessell, et al.

Client Columbia (0575) File No. 57477-A-PCT-US Atty. JPW/MVM

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JUL - 6 2004

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Applicants: Thomas Jessell et al.
U.S. Serial No.: 109/820,598
Filed: March 29, 2001
Exhibit VII

57477-A-PCT-US

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.

1 Mo: 8/14/04
2 Mo: 9/14/04
3 Mo: 10/14/04
4 Mo: 11/14/04
5 Mo: 12/14/04
6 Mo: 1/14/05

JUL 19 2004

EXAMINER	
ART UNIT	PAPER
	06292004

DATE MAILED: 7/14/04

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

This Notice is in response to the paper filed May 14, 2004.

The proposed reply filed on May 14, 2004 has not been entered because it is unsigned.

Since the above mentioned reply appears to be bona fide, applicant is given a TIME PERIOD of ONE (1) MONTH or THIRTY (30) DAYS from the mailing date of this notice, whichever is longer, within which to supply the omission or correction in order to avoid abandonment. EXTENSIONS OF THIS TIME LIMIT MAY BE GRANTED UNDER 37 CFR 1.136(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cochrane Carlson, Ph.D. whose telephone number is 571-272-0946. The examiner can normally be reached on 7:00 AM - 4:00 PM, off alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

PTO-90C (Rev.04-03)

Applicants: Thomas Jessell et al.
U.S. Serial No.: 109/820,598
Filed: March 29, 2001
Exhibit VIII

UNITED STATES PATENT AND TRADEMARK OFFICE

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09/820,598 ✓	03/29/2001	Thomas M. Jessell	57477-A-PCT-US/JPW/MVM	5690

7590 07/14/2004

Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
CARLSON, KAREN C	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Dkt. 57477-A-PCT-US/JPW/MVM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Thomas M. Jessell et al.

Serial No.: 09/820,598 Group Art Unit: 1653

Filed: March 29, 2001 Examiner: K. Carlson, Ph.D.

For: GENE ENCODING MNR2 AND USES THEREOF

1185 Avenue of the Americas
New York, New York 10036
August 16, 2004

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

COMMUNICATION IN RESPONSE TO JULY 14, 2004 NOTICE

This Communication is submitted in response to a July 14, 2004 Notice issued by the United States Patent and Trademark Office ("USPTO") in connection with the above-identified application. A copy of the Notice is attached hereto as **Exhibit A**. The Notice provides a one-month period for filing a response. Therefore, a response to the Notice was due August 14, 2004. However, since August 14, 2004 was a Saturday, a response on the next succeeding day which is not a Saturday, Sunday or Federal holiday, i.e. Monday, August 16, 2004, is considered timely under 37 C.F.R. §1.7. Accordingly, this Communication is being timely filed.

REMARKS

The Examiner objected to applicants' May 11, 2004 reply to the February 11, 2004 Office Action and stated that applicants'

reply will not be entered because it is allegedly not signed. Applicants note the date of May 14, 2004 erroneously attributed to the May 11, 2004 Amendment.

Further to an August 13, 2004 telephone conference between myself and Mark Polutta, Esq. of the USPTO Office of Patent Legal Administration, Mr. Polutta stated that the July 14, 2004 Notice will be withdrawn and that therefore, a response to the Notice is not required. Mr. Polutta stated that a new communication will be sent by the USPTO in connection with the subject application.

Applicants submit this Communication in order to make of record the August 13, 2004 telephone conference between myself and Mr. Polutta, wherein Mr. Polutta stated that a response to the July 14, 2004 Notice is not required.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

8/16/04

John P. White
Reg. No. 28,678

Date

57477-A-PCT-US

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JPW

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ART UNIT	PAPER
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Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

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EXAMINER	
CARLSON, KAREN C	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 07/14/2004

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FILE

Applicant Thomas M. Jessell, et al.

Client Columbia (0575) File No. 57477-A-PCT-US Atty. JPW/MVM

Date August 16, 2004

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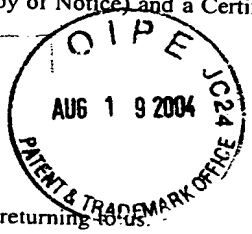
AUG 2 4 2004



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Applicants: Thomas Jessell et al.
U.S. Serial No.: 109/820,598
Filed: March 29, 2001
Exhibit X